DISSERTATION TITLED

"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"** is a bonafide work done by **DR. M.BALACHANDRAN**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, during March 2014 to August 2014 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2012 - 2015.

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DECLARATION

I solemnly declare that the dissertation entitled **"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"** is done by me at Madras Medical College, Chennai-3 during March 2014 to August 2014 under the guidance and supervision of **Prof. S.TITO, M.D.,** to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.**

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ABBREVIATIONS

.rtPA	-	Recombinant tissue plasminogen activator
25-(OH) Vit D	-	25-hydroxyVitamin D
ACA	-	Anterior cerebral artery
CBG	-	Capillary blood glucose
CMIA	-	Chemiluminescent microparticle immunoassay
CNS	-	Central nervous system
CT	-	Computed tomography
CVA	-	Cerebrovascular accident
DWI	-	Diffusion weighted MRI
ECG	-	Electrocardiogram
ICA	-	Internal carotid artery
ICP	-	Intra cranial pressure
iNOS	-	Inducible nitric oxide synthase
MCA	-	Middle cerebral artery

MRI	-	Magnetic resonance imaging
NIHSS	-	National Institutes of Health Stroke Scale
OCP	-	Oral contraceptive pills
PCA	-	Posterior cerebral artery
PTH	-	Paratharmone
TIA	-	Transient ischemic attack
UV-B	-	Ultra violet ray- B

CONTENTS

"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"

ABSTRACT:

Stroke remains to be one of the leading causes of the mortality worldwide. The majority of the stroke as a result of occlusion of the blood supply to the brain leading to cerebral infarction (Ischemic stroke). The Vitamin D deficiency is present worldwide, and recent studies found that there is direct correlation between Vitamin D deficiency and ischemic stroke.

The hyperglycemia on admission is associated with poor outcome in the patient with ischemic stroke. The hyperglycemia is associated poor salvage of the ischemic penumbra. The hyperglycemic ischemic stroke patient are associated with higher infarct volume on admission, a greater progression of the ischemic stroke, resulting in higher final infarct volume when compared with the patient who are euglycemia on admission.

In this study, ischemic stroke patients fitting into the criteria are selected, and the Vitamin D are assessed, the glycemic status on admission is correlated with the infarct volume on admission and on 3^{rd} to 7^{th} day of the stroke by using MRI-Diffusion weighted images of the brain.

Conclusion:

In our study the results are Vitamin D deficiency common in ischemic stroke, and the hyperglycemia on admission is associated with higher infarct volume on admission, a greater progression of the ischemic stroke, resulting in higher final infarct volume when compared with the patient who are euglycemia on admission.

KEY WORS:

ischemic stroke, infarct volume, hyperglycemia, Vitamin D, MRI-Diffusion weighted image, ischemic penumbra

INTRODUCTION

Stroke remains to be the one of the leading cause of death in the world, although the incidence of the stroke seems to be decreasing because of the advances in the management and availability of preventive measures. Ischemic stroke contributes for the larger number of stroke cases, in which, the partial or complete occlusion of the regional vasculature of the brain leading on to the infarction of the brain tissue.

Vitamin D, actually a pro-hormone, is synthesized in the human body, in the presence of sunlight (UV–B).The current lifestyle of reduced exposure to the sunlight leads increased risk for the development of Vitamin D deficiency worldwide.

Vitamin D is required for the calcium homeostasis, other functions including role in muscle contraction, immune functions, nerve conduction. Vitamin D deficiency is at risk for the development of various neurological diseases like dementia, Alzheimer diseases, multiple sclerosis, stroke.

Its functions include decreasing renin- angiotensin-aldosterone activity, anti- inflammatory, anti-atherosclerotic action, decreasing vascular calcification. Other role includes decreasing the protein excretion in the urine, role in neuro-protection by insulin like growth factor-1 synthesis. Vitamin D

deficiency leads to systemic hypertension and increases in the stroke incidence.

Acute hyperglycemic response to stress has been recognized since Claude Bernard's observations more than a century ago.[1] Stress hyperglycemia or in hospital hyperglycemia is present any blood glucose valve >140 mg/dl. The mechanism responsible for stress hyperglycemia includes stimulation of HPA axis during to the stress for the stroke event. This leads onto increased cathecolamines, cortisol, glycogen, resulting in increased lipolysis, proteolysis, glycogenolysis, gluconeogenesis. Hyperglycemia is associated with abnormal immune function, hemodynamic, electromyocardial disturbances and increased infection rate.[2]

Regardless of the time period between the stroke and glucose estimation, elevated blood sugar levels is common in the ischemic stroke, irrespective of the diabetic status. Admission hyperglycemia usually correlates with increased infarct size on admission and poor clinical outcome.

This study is to assess the vitamin D levels in patients admitting for ischemic stroke and to look for Vitamin D level in these group of populations, to find correlation between glycemic status and stroke extent / territory during admission and hospital stay (3 to7th day) by using multimodal CT/ MRI Brain scans.

AIM AND OBJECTIVES

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- To study the Vitamin D levels in the ischemic stroke.

- To assess the relation between glycemic status and ischemic stroke infarct volume and their territory during admission & course of stay in the hospital (3 to 7^{th} day)

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Several centuries before Hippocrates mentioned in his description of stroke as an apoplexy which means – “thunder struck or sudden depriving of one’s sense”. He mentioned that people of ages between forty to sixty or more at risk when compared to fellow person. Galen (131- 201 AD), based on dissections of animals, was the first person to described the structure of brain, its anatomy and its blood supply.

Johann Jacob Wepfer (1620- 1695) described that the sudden onset of this apoplexy is due to the blood vessel diseases of brain where in the blood supply to the brain (carotid and the vertebral arteries) are affected. He showed apart from occlusion of these vessels, bleeding from these vessels into the brain was an important cause of apoplexy.

Thomas Wills, a neuro-anatomist proposed the cerebral blood vessel anastomoses at the base of brain(CEREBRAL ANASTOME), and named after him – CIRCLE OF WILLIS. He also described transient ischemic attacks, existence of occlusion of carotid artery, the embolus as etiology for the stroke.

John Abercrombie published paper on the apoplexy in that he stated headache, stupor, paralysis as the features of apoplexy. Following this, several studied had been done and different stroke syndrome established, and during twentieth century, there was several advanced technology allowed better visualization of the brain anatomy and there functions, and pathological lesions affecting the brain.

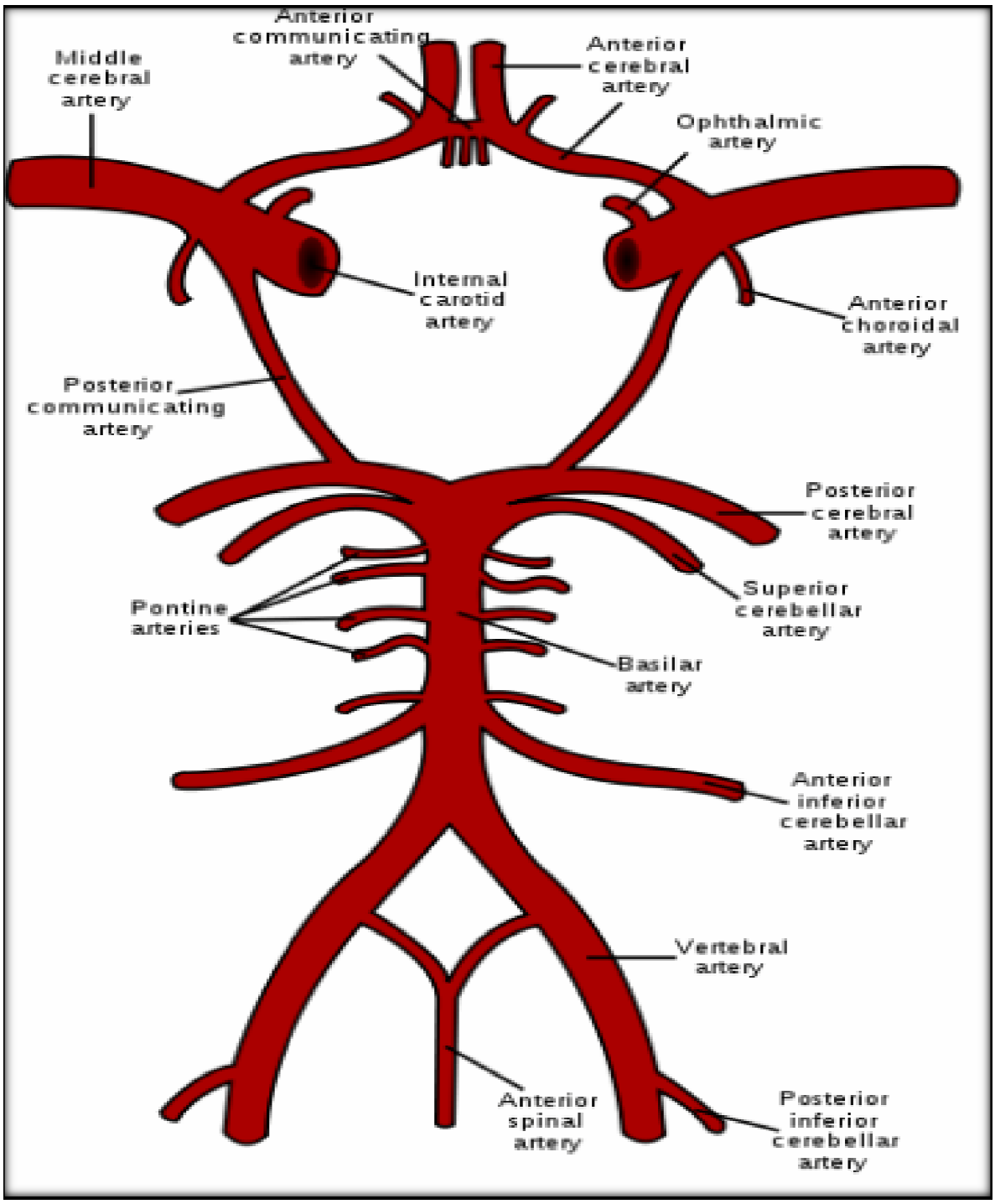
Moniz (1874-1955), Portugal neurosurgeon, surgically exposed & ligated the cranial artery in the neck, then 30% sodium iodide injected and skull films taken at regular intervals. Seldinger, from Sweden, devised technique of modern angiography, in which small catheter introduced into artery over a flexible guide wire after withdrawing the needle.

In 1960, Hounsfield from Britain, originated the concept of Computed Tomography (CT). In the mid 1980, MRI proved superior to CT in picking up the old hemosiderin containing hemorrhages, vascular malformation, lesion involving posterior cranial fossa, lesion abutting on bony surfaces.

Franklin, in early 1961, demonstrated the uses of ultrasound in imaging the extra cranial carotid vessels. At the end of 20th century, advanced imaging with CT, MRI spectroscopy helped in the localisations, severity and potential reversibility of brain ischemia. Vascular lesions can be assessed better by using CT and MR angiography.[3,4]These advances will help in the better management of the stroke in upcoming future.

BLOOD SUPPLY OF BRAIN:

Blood supply for the brain is from two internal carotid artery & two vertebral artery. At the base of brain, these blood vessels anastomosis forming circle of WILLIS. Of the total weight of body, brain contributes for about 2%. Of the total cardiac output, around 20% of the blood enters the brain.



CIRCLE OF WILLIS

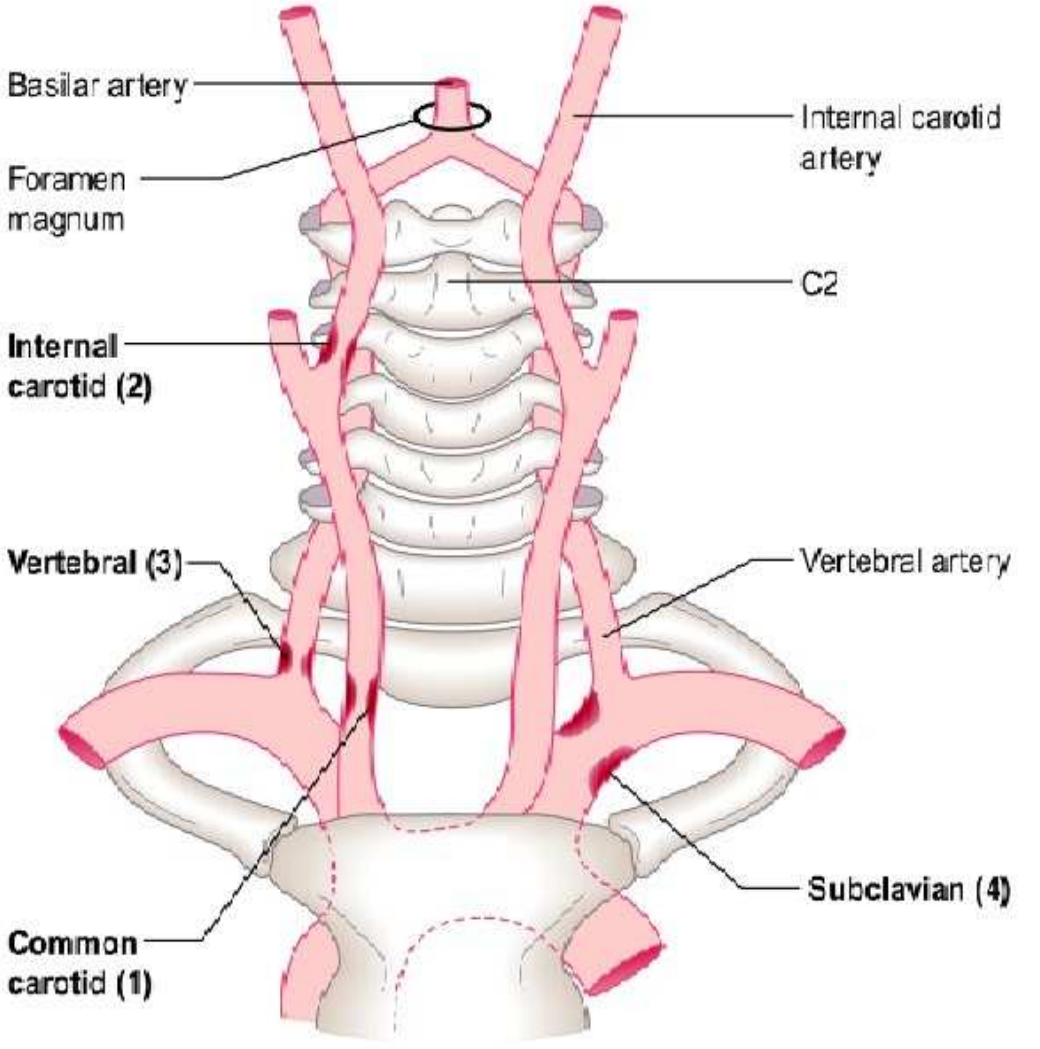
MAIN BLOOD SUPPLY TO BRAIN:

1. Internal carotid artery (Right & Left)
2. Vertebral artery (Right & Left)

Circle of Willis: is formed anteriorly by two ACA, which is connected by anterior communicating artery anteriorly, posteriorly by two PCA, communicating with anterior circulation by the posterior communicating artery.

INTERNAL CAROTID ARTERY (ICA):

- The internal carotid artery arises from common carotid artery, which in turn arises from brachiocephalic artery on right side & aortic arch on the left side.
- Internal carotid artery start at thyroid cartilage level, runs into neck without branching, enters into base of the skull through the foramen lacerum. Then it enter into cavernous sinus, then comes out of the cavernous sinus just medial to the anterior clinoid process.
- The branches includes –
    - ophthalmic artery,
    - posterior communicating artery,
    - anterior choroidal artery,
    - anterior cerebral artery,
    - middle cerebral artery.



Principal sites of stenoses in extracerebral arteries (shown in bold, 1 to 4).

- Ophthalmic artery is the first branch arising from internal carotid artery, supplies eye and other structures of the orbit.
- Posterior communicating artery is the next branch of ICA, which runs back to join the posterior cerebral artery, supplying optic chiasma, optic tract, hypothalamus, midbrain, thalamus.

- Anterior choroidal artery arises from distal region of ICA supplying the internal capsule, optic tract, basal ganglia, thalamus, lateral geniculate body, midbrain, proximal optic radiation.
- Middle cerebral artery enters sylvian fissure, before entering it gives of deep cerebral branches (Lenticulostriate branches). In the sylvian fissure, the MCA divides into superior & inferior division supplying the lateral part of the cerebral cortex. The lenticulostriate branches supply the putamen, outer globus pallidus, internal capsule (posterior limb).
- Vertebral artery arises from the proximal subclavian artery, then it ascends upward reaching the transverse foramina of sixth & second vertebrae, then it join with the vertebral artery of the other side to form basiliar artery. The branches of vertebral artery includes – anterior spinal artery, posterior spinal artery, posterior inferior cerebellar artery, small penetrating branches to medulla. The posterior inferior cerebellar artery supplies inferior vermis, inferior and posterior surfaces of the cerebellum, brainstem.
- Basilar artery ascends up to the pons & in the inter-peduncular cistern where it divide into posterior cerebral artery. The other branches include labyrinthine artery; anterior inferior cerebellar artery which supply the rostral cerebellum, brainstem, inner ear; the superior

cerebellar artery supplying the brainstem, cerebellar hemisphere (superior part),vermis, dentate nucleus; the posterior cerebral artery.

- The posterior cerebral artery winds rounds the midbrain near the occulomotor nerve, and supplies temporal lobe (inferior part), occipital lobe. The deep branches of the PCA supply mainly midbrain, thalamus, hypothalamus, geniculate bodies (thalamostriate branches). The common variation of the posterior cerebral artery is the in about 15% people, PCA is the direct continuation of the posterior communicating artery (PCoM).

COLLATERAL BLOOD SUPPLY IN THE BRAIN:

In the normal situation, the anterior two-third of the cerebral circulation is supplie by the internal carotid artery and the posterior one – third is supplied by the vertebral artery. In the cases of blood vessels occlusion, collateral develop distal to the site of occlusion, and the collateral development depends on the vessels occluded, and whether the other artery are free of disease or not.

Other regions of collateral blood flow are:

1. Leptomeningeal anastomoses
2. Around the orbit
3. Parenchymal anastomes

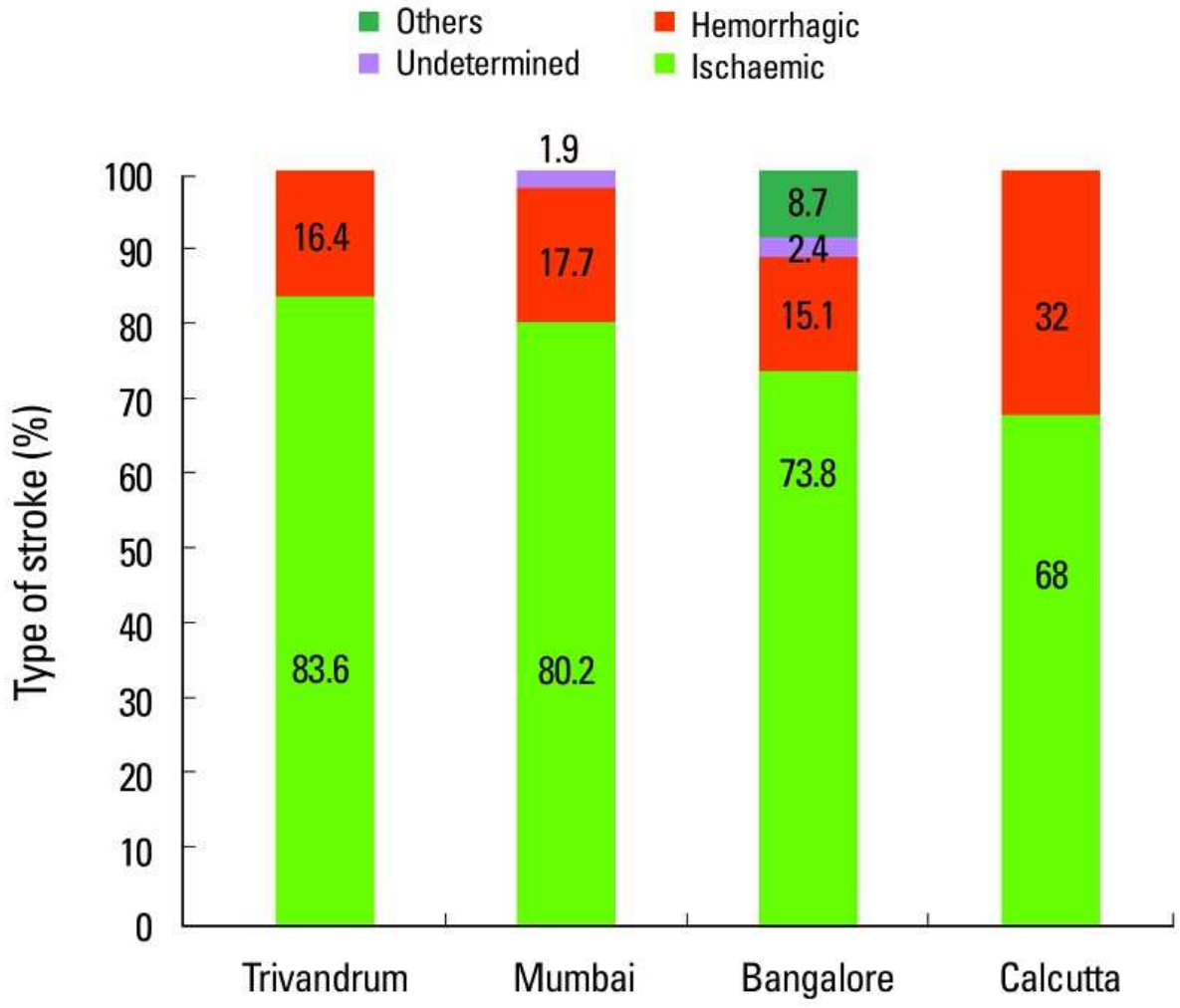
Venous drainage of the brain:

1. Superficial cerebral veins
2. Deep cerebral veins

Both these veins drains into the dural venous sinuses, which further drains into the internal jugular vein . The cerebral veins lacks valves, they are thin walled, & the blood flow in these veins are in the same direction as that of the neighboring arteries.[5]

EPIDEMIOLOGY OF THE STROKE:

Apart from the ischemic heart disease & cancer, stroke remains one the most leading causes of the death in the United States. Yearly around seven lakhs of stroke occurring – of which 6/7 th are ischemic strokes and remaining 1/7 are hemorrhagic stroke. It remains the leading causes of the disability in adults. The calculated economic impact on the society is about $40 billion,[6] both directly in health care & by the loss of income. By the various preventive measures the has been a steady decrease in the stroke occurrence to 54% over the last 30 years, in USA. Incidence of stroke in the age group of 75-84 years in different countries include 1054 (France), 2062 (Sweden). There was about 38% increase in the stroke in the women from the year 1975 to 1978 and 1983 to 1985.[7]

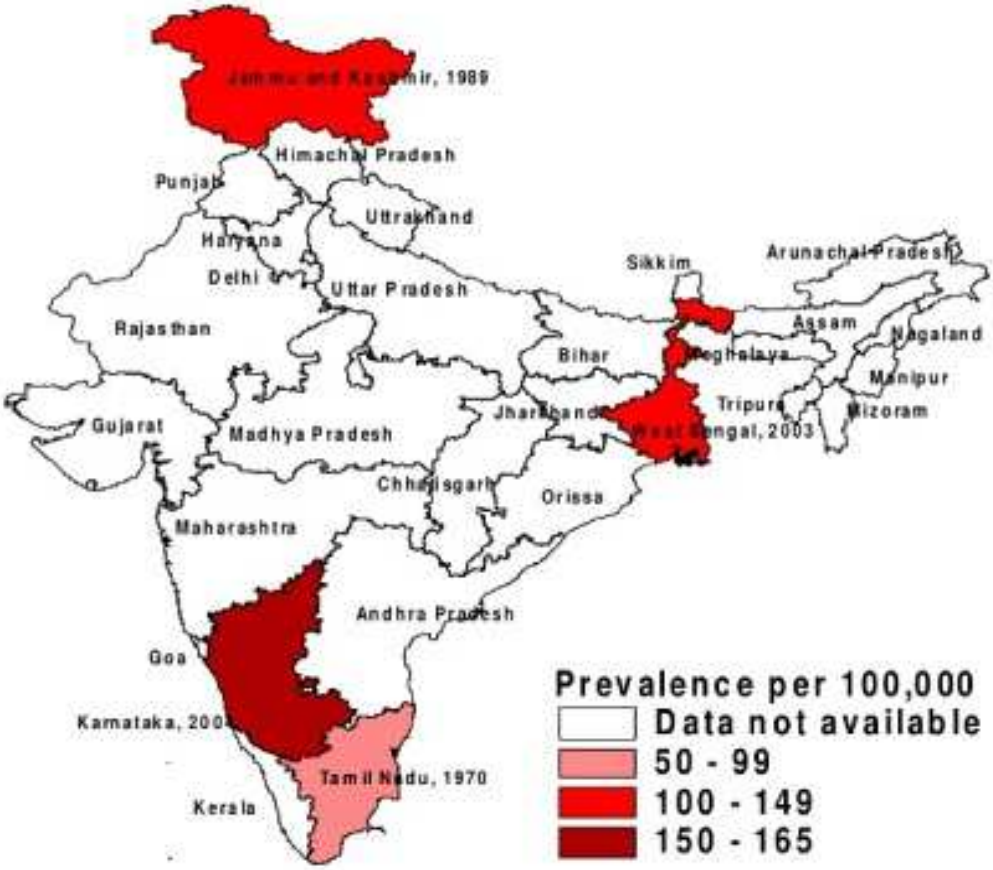


Distribution of stroke subtypes in the various incidence studies.

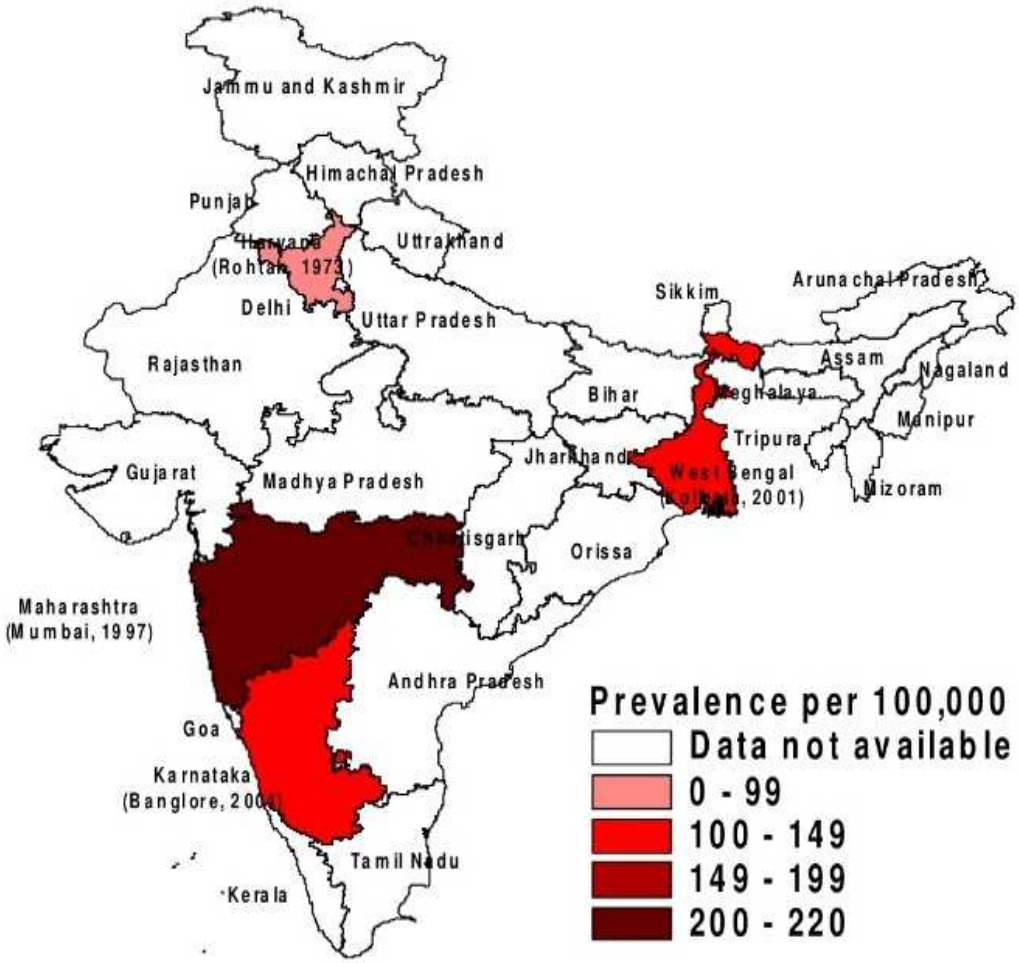
In India, community based stroke study was done in Vellore (1969-71), Rohtak (1971-74). The stroke contributes for around 4.6% of medical cases, 20% of all the neurological cases admitted to the hospital.[8] The Indian studies details are as below;

1) Incidence of stroke - 119 to 145 per lakhs of population,
2) Prevelance of stroke – 84 to 262 per lakhs of population (rural),
   334 to 424 per lakhs of population (urban)
3) Cases fatality rates – around 25% (urban population), 37% (rural population) are died due to stroke and its complication during 28 days of stroke. Mortality is highest in Kolkata studies (mortality rate – 42%).
4) IV thrombolysis of stroke –11% of the stroke.[9]
5) Stroke subtypes – 68% cerebral infarct, 32% cerebral hemorrhage.[10]
6) Stress hyperglycemia prevelance – 14 – 60%.[12]
7) Stroke contributes for 1.2% of all death in the country.[11]

PREVALANCE RATE FOR STROKE IN RURAL INDIA (1970-2004)



PREVALANCE RATE FOR STROKE IN URBAN INDIA (1973-2004)



Stroke, the most common neurological diseases in adults, presents with clinical features of sudden onset (in a matter of second) of neurological deficit. Stroke can be divided into two main subtypes – ischemic or hemorrhagic stroke. Ischemic stroke arises as a result of occlusion of blood vessels to the brain which leads to sudden cut off of the blood supply leading cerebral infarction.

Ischemic stroke is further divided into thrombotic stroke & embolic stroke. Based on underlying etiology, ischemic stroke, can arises from (1) atherosclerosis of large cerebral blood vessels, (2) occlusion of small cerebral vessel within brain parenchyma, (3) cerebral embolism. Several other causes of brain parenchyma infarction includes arterial dissection, vasculitis, hyper-coagulable state, cortical vein thrombosis.

Transient ischemic attack (TIA), is defined as temporary neurological deficit caused by cerebrovascular disease, characterized by no clinical or imaging trace, with complete recovery occurring within 24 hours.[13] Onset of stroke differs in ischemic and embolic stroke. The thrombotic stroke evolves over hours to days, in a saltatory fashion. In the embolic stroke, the onset is sudden, peak at once. The static onset & evolves over minutes is a feature in hemorrhagic stroke.

Stroke mimics:

Various conditions like Migraine, Todd paralysis (seizure), Brain tumor, abscess will be imitating stroke and these condition should be considered in differential diagnosis.

ISCHEMIC STROKE - RISK FACTORS:

1. NON -MODIFIABLE:

a) Age : the most important risk factor of the stoke, & the risk doubles after 55 years, for every decade.

b) Sex : incidence and mortality of the stroke is higher in male gender compared to that of female gender.

c) Genetic factors : chromosome 12 polymorphism

d) Race / Ethnicity : Afro Carrribeans> Asians > Europeans have stroke incidence in the decreasing order

2. MODIFIABLE:

a) Diabetes mellitus : 1.8 to 3.5 times increases in the stroke incidence, with most of them are lacunar strokes. Hyperglycemia and insulin resistance are the other risk factors.[14]

b) Systemic hypertension : the most important risk factor in the development of ischemic stroke. The incidence is three times higher when compared to normotensive people. Recent studies revealed that 46%

reduction in the stroke incidence for every 7.5 mmHg reduction in diastolic BP. Around 40% of strokes have a blood pressure of greater than 140mmHg.[15,16,17]

c) Dyslipidemia (elevated LDL cholesterol, elevated triglycerides) : Statin therapy reduce the stroke incidence by 20 -30%, because of its action of stabilizing the plaque, anti thrombotic action, improved endothelial function, and by reducing the inflammation.[18]

d) Cigarette smoking : increases the risk of all types of stroke. The risk is highest in the younger group, with risk proportionate to the number of cigarettes smoked.[19,20]

e) Alcohol intake : the risk is variable. Risk is reduced with low to moderate consumption. Higher level of consumption increases the incidence of hemorrhagic stroke.

f) Obesity : along with smoking, a BMI of > 25 kg/m2, account for 60% of stroke, in the group of men upto sixty five years.

g) Transient ischemic attack (TIA) : 10 times higher risk of stroke when compared to person without stroke.

h) History of Stroke in the past

i) Asymptomatic carotid bruit/stenosis

j) Cardiac illness : the presence of left ventricular hypertrophy by ecg increases ischemic stroke risk by 10 fold,[21,22]presentation of congestive heart failure increases stroke incidence by nine fold. Atrial fibrillation raises the

risk of embolic stroke by 5 to 7 times than age matched population of normal cardiac rhythm. Other risk factors include mitral valve prolapsed, prosthetic valves, endocaritis, congenital heart diseases.[23]

k) Aortic arch atheromatous diseases

l) increased fibrinogen level

m) Raised homocysteine level

n) Decreased serum folate

o) increased anti-cardiolipin antibodies

p) Oral contraceptive use : risk is higher in young women who is taking estrogen content of more than 50 mcg. OCP increases ischemic stroke secondary to enhance platelet aggregation & alteration in clotting factors.[24]

q) anticoagulation therapy: increases risk of hemorrhagic stroke.

r) intake of low potassium, reduced serum potassium level

CLASSIFICATION OF STROKE

Based on the pathogenesis:

(A) Ischemic stroke –

(i) With cerebral infarction:

1. Cerebral thrombosis with or without atherosclerosis
2. Cerebral embolism
3. Cerebral venous thrombosis
4. Vasculitis
5. Cerebral anoxia
6. Hematological disorder
7. Complications due to angiography
8. Aneursymal dissection affecting the brachiocephalic vessels
9. Systemic hypotension, anoxic encephalopathy
10. Unknown cause

(ii) With cerebral ischemia:

1. Transient ischemic attacks(TIA)
2. Artery to artery embolism
3. Paradoxical embolism
4. Cardiac arrhythmias
5. Arterial hypotension
6. Migraine / Sub-arachnoid hemorrhage causing vasospasm

7. Idiopathic causes (drugs, consumptional coagulopathy, cerebral malaria, Behcet's syndrome, cerebral amyloid angiopathy, hyperviscosity, hyperhomocysteinemia)

(b) Hemorrhagic stroke:

1. hypertensive cerebral hemorrhage
2. rupture aneurysm
3. trauma
4. blood dyscrasias
5. anticoagulation therapy or thrombolytic therapy
6. bleeding in the brain tumors
7. miscellaneous

(c) Stroke of undetermined origin:

1. leukariosis
2. Moyamoya disease
3. Fibromuscular dysplasia
4. Binswanger's disease
5. Aortic arch syndrome
6. Winiwarterbuerger disease

(B) Clinical classification:

(1) Based on arterial territory:

(a) Anterior circulation stroke:

- Anterior cerebral artery (ACA) syndrome

- Middle cerebral artery (MCA) syndrome

(b) Posterior circulation stroke:

- Vertebro basilar artery syndrome

- Posterior cerebral artery syndrome

(2) Based on clinical manifestations:

(a) Transient ischemic attack – Focal neurological deficit with complete recovery within 24 hours

(b) Reversible ischemic neurological deficit – neurological deficit with complete recovery within one week.

(c) Evolving stroke : stuttering or gradual development of deficit

(d) complete stroke: rapid onset of stroke, with persistent neurological

Deficit which does not progress beyond 96 hours.[25]

CAUSES OF STROKE IN DIFFERENT AGE GROUP

CEREBROVASCULAR DISEASES CHARACTERISTIC OF EACH AGE PERIOD

1. Prenatal circulatory diseases leading to
   a. Porencephaly
   b. Hydranencephaly
   c. Hypoxic-ischemic damage
   d. Unilateral cerebral infarction
2. Perinatal and postnatal circulatory disorders resulting in
   a. Cardiorespiratory failure and generalized ischemia—*état marbre*
   b. Periventricular infarcts
   c. Matrix hemorrhages and ischemic foci in premature infants
   d. Hemorrhagic disease of the newborn
3. Infancy and childhood: vascular diseases associated with
   a. Ischemic infarction
   b. Congenital heart disease and paradoxical embolism
   c. Moyamoya disease
   d. Bacterial endocarditis, rheumatic fever, lupus erythematosus
   e. Sickle cell anemia
   f. Mitochondrial disorders (MELAS)
   g. Homocystinuria and Fabry's angiokeratosis
4. Adolescence and early adult life: vascular occlusion or hemorrhage with
   a. Pregnancy and puerperium
   b. Estrogen-related stroke
   c. Migraine
   d. Vascular malformations
   e. Premature atherosclerosis
   f. Arteritis
   g. Valvular heart disease
   h. Sickle cell anemia
   i. Antiphospholipid arteriopathy, plasma C-protein deficiency and other coagulopathies
   j. Moyamoya, Takayasu diseases
   k. Arterial dissections
   l. Amyloid angiopathy
5. Middle age
   a. Atherosclerotic thrombosis and embolism
   b. Cardiogenic embolism
   c. Primary (hypertensive) cerebral hemorrhage
   d. Ruptured saccular aneurysm
   e. Arterial dissection
   f. Fibromuscular dysplasia
6. Late adult life
   a. Atherosclerotic thrombotic occlusive disease
   b. Embolic disease
   c. Lacunar stroke
   d. Brain hemorrhage (multiple causes)
   e. Multiinfarct dementia
   f. Binswanger disease

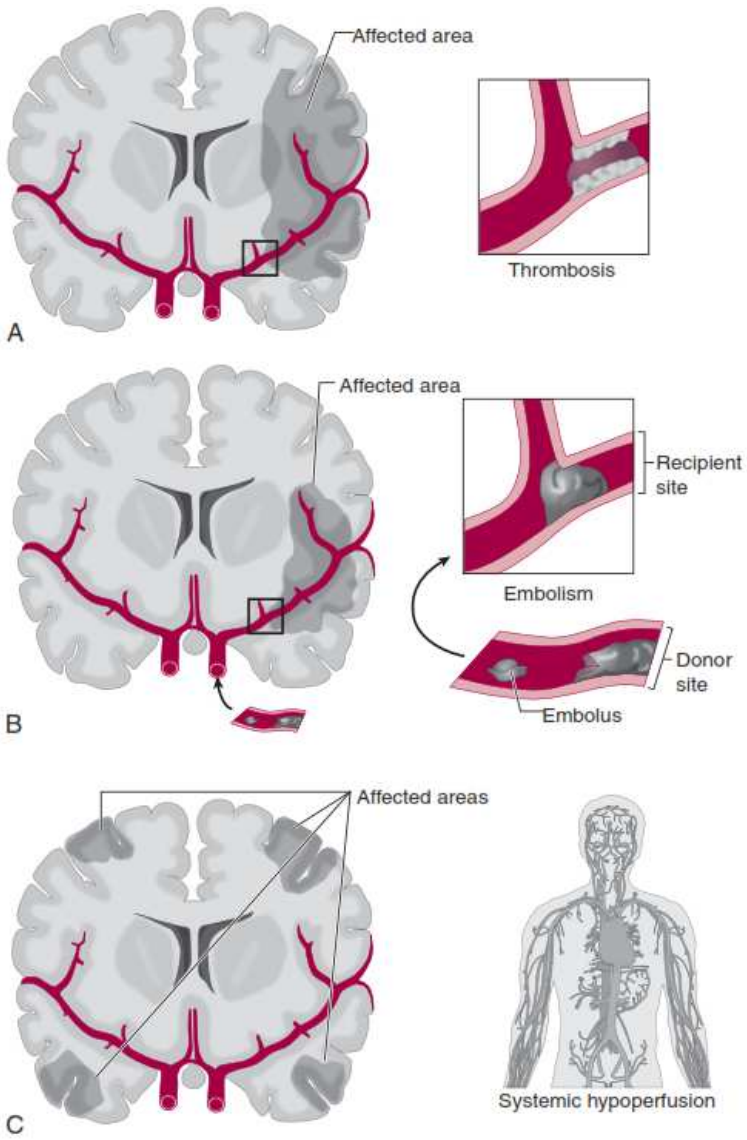
CAUSES OF CEREBRAL VASCULAR OCCLUSION AND ISCHEMIC STROKE:

- **Cerebral vessel athero-thrombosis :**

Cerebral infarction occurs as results of – thrombus formed on plaque, artery to artery embolism, water shed infarct. Larger vessel involved in the site of branching point of the larger vessel. The sites involved are origin of the internal carotid artery from common carotid, the junction between vertebral & basiliar artery; middle cerebral artery involved mainly in the stem or its main bifurcation. Small vessel atherosclerosis mainly affects the lenticulo-striate branches (of middle cerebral artery), thalamo-striate branches (of posterior cerebral artery). This type of stroke evolves in stuttering fashion or intermittent progression over hours to days. Some of these stroke can also present in episodic fashion. Most of stroke this stroke occurred during sleep as a result of vascular stasis.

• Cerebral embolism : Either from the cardiac source or from the artery to artery embolism. Cardioembolism accounts for around twenty percentage of all ischemic strokes, arising dueto embolism of thrombotic material forming on the endothelial surface of the heart. These strokes are sudden in onset, with maximum neurologic deficit atonce. The fragmentation of thrombus or quick lysis produces only transient ischemicattack (TIA).

PATHOGENESIS OF DIRRERENT TYPES OF ISCHEMIC STROKE



Illustrations of the three major causes of brain ischemia. (**A**) Thrombosis. The *insert* shows a thrombus in an atherosclerotic artery leading to a brain infarct, (**B**) Embolism. A thrombus that originated in a donor source embolized to the recipient site (shown in the insert) causing an embolic brain infarct, and (**C**) systemic hypoperfusion. Infarcts are in border-zone regions.

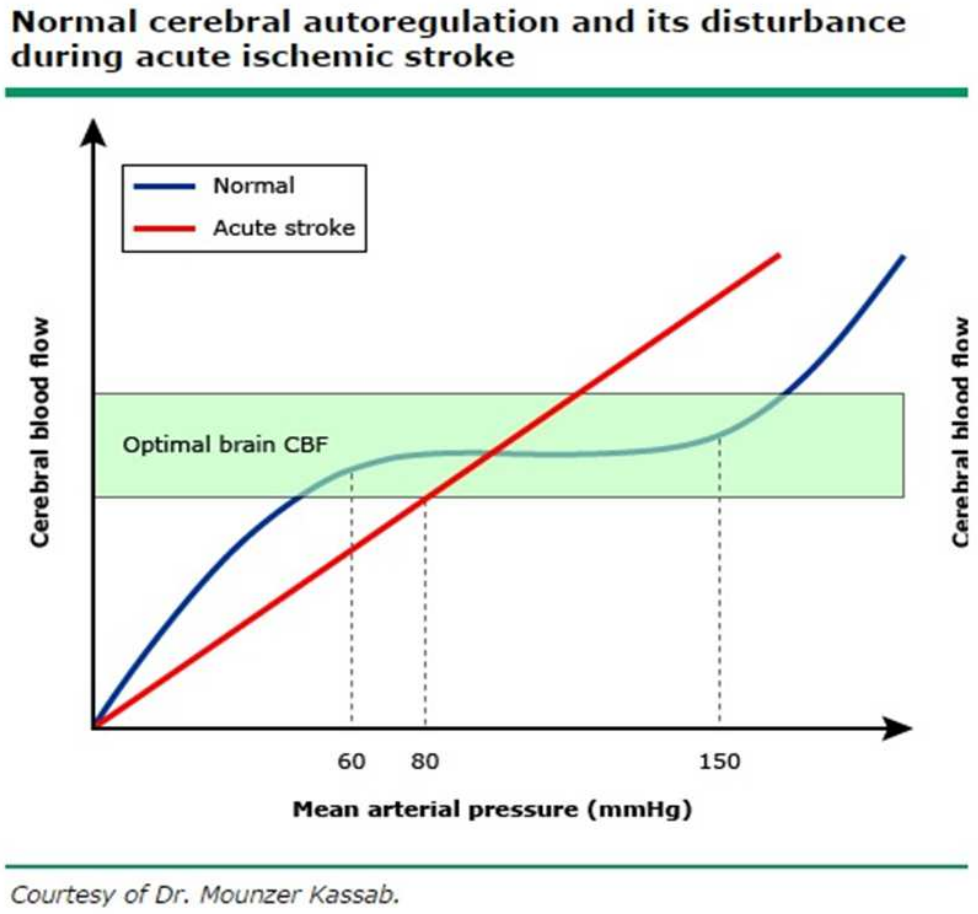
PATHOPHYSIOLOGY OF STROKE:

CEREBRAL AUTOREGULATION

Normally blood flow to the brain is mainly depend up on the amount of vascular resistance within cerebral blood vessels, which is related to their circumference.[26]Dilation of blood vessels leads to increased cerebral blood flow, whereas constriction of vessels has the opposite effect. Cerebral perfusion pressure also determine the cerebral blood flow.

Cerebral autoregulation is the phenomenon by which maintaining the cerebral blood flow at a relatively constant rate despite variations in perfusion pressure. The mechanism by which auto-regulation occurs is not well understood, and may involve multiple pathways

There are evidences which suggests that the smooth muscle in cerebral vessels can respond directly to changes in perfusion pressure, contracting when pressure increases and relaxing when pressure decreases. Reductions in cerebral blood flow may lead to cerebral vasodilatation due to release vasoactive substances, although the substance responsible for this have not been identified. Nitric oxide which releasing from vascular endothelium appears to play a role in autoregulation.



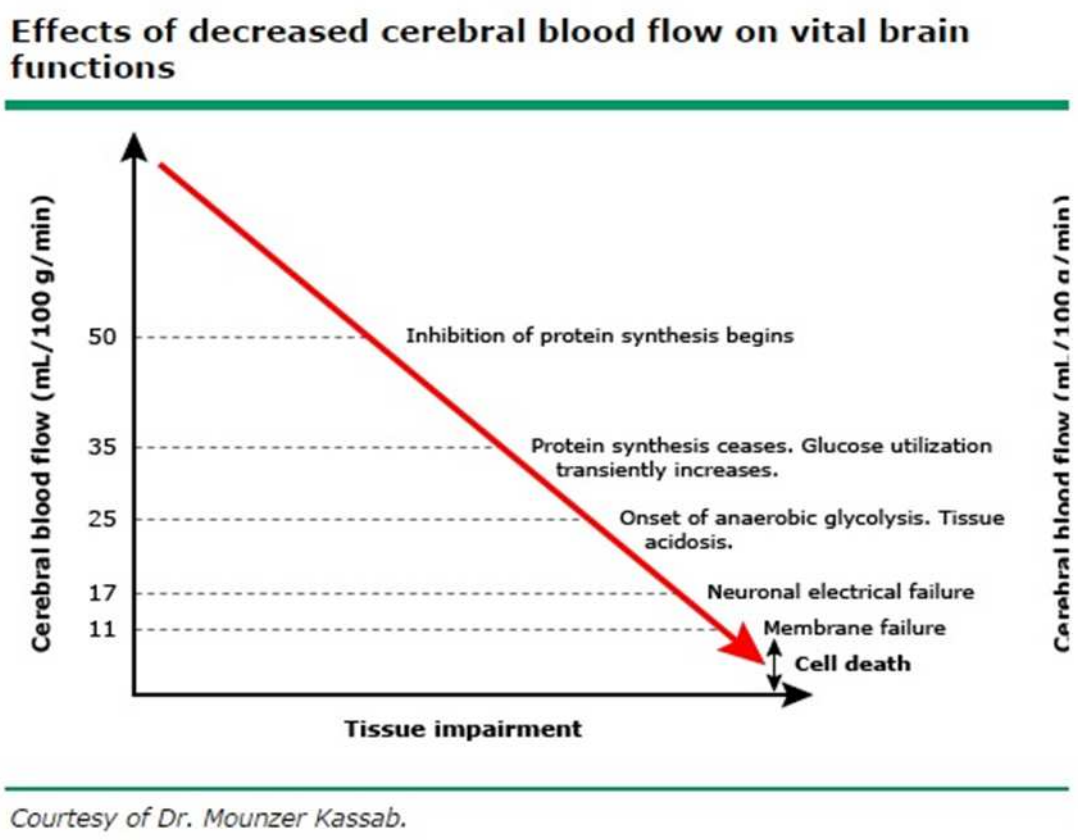
Courtesy of Dr. Mounzer Kassab.

Cerebral blood flow is maintaining by autoregulation which typically occurs within a range of 60 to 150 mmHg of mean arterial pressure. The upper and lower limits vary between individuals, however. Beyond this range, the brain is unable to compensate for changes in perfusion pressure, and the cerebral blood flow increases or decreases passively with corresponding changes in pressure, resulting in the risk of ischemia at low pressures and edema at high pressures

Cerebral autoregulation during stroke

Cerebral auto regulation is impaired due to some disease conditions,[27,28] which includes ischemic stroke also .when cerebral perfusion pressure decrease there will be cerebral vascular dilatation and when it fall below the compensatory capacity of the brain it will lead to decrease in the cerebral blood flow . Initially, the oxygen extraction fraction is increased in order to maintain levels of oxygen delivery to the brain. As the cerebral blood flow continues to fall, other mechanisms come into play.

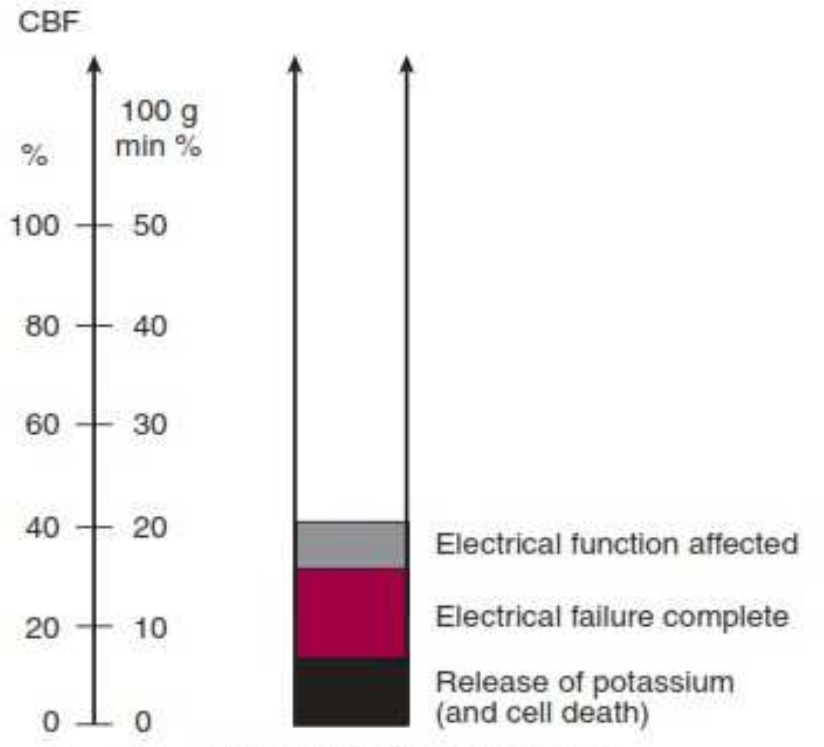
In patient with hypertension auto regulation is usually occur at higher arterial pressures. Reduction of blood pressure to normal levels could actually exacerbate the derangement to autoregulation that occurs during stroke and lead to a further decrease in cerebral blood flow .



CONSEQUENCES OF REDUCTION IN BLOOD FLOW DURING STROKE

The human brain is very much sensitive to even a short durations of ischemia. Even though brain is only 2 to 3 percent of total body weight the blood flow it receives is about 20 percent of the total cardiac output.

The brain has no energy stores of its own, and therefore it depend on the blood for their delivery. So evena brief deprivation can lead to death of the affected brain tissue. During stroke, reduction of blood flow to brain results in a deprivation of glucose and oxygen .



Thresholds of brain ischemia.

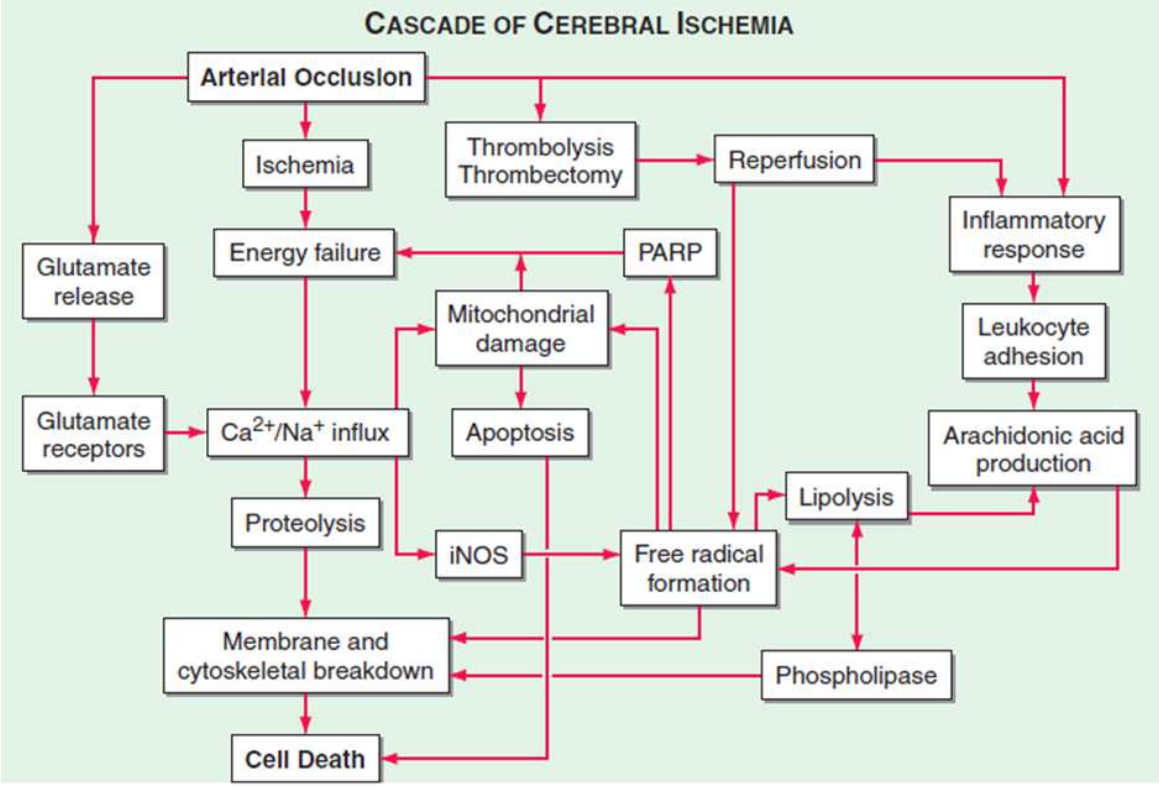
Commonly strokes are due to ischemia, which affecting the small part of the brain and mainly affecting a single blood vessel and its branches. Region which commonly involved is area supplied by the same vessel which is immediately surrounding the vessel. If the ischemia is prolonged in this area, cells will die by necrosis and the peripheral area which receives

nutrients and oxygen by collateral vessel will not die immediately, which can be revived by timely intervention and restoration of blood flow. This area which surrounds the dead cells is known as ischemic penumbra. And the area underwent necrosis is known as infarct.

Mechanisms of ischemic cell injury and death :

A sequence of events following the brain ischemia which leads to brain cell death. The possible mechanisms are

1. ATP depletion
2. Na+ ,K+ and Ca2+ ionic concentration changes
3. Increase amount of lactic acid which leads to acidosis
4. Oxygen free radicals
5. Proteolytic enzymes
6. Accumulation of water inside the cell



As a consequence of the electrical failure that occurs as a result of ischemia, there will be increased secretion of excitatory neuro transmitter at the synapse will cause the glutamate receptor activation and lead to out flow of the potassium and inflow of the sodium and calcium ion .It will lead to variety of effects. The main subtypes of glutamate receptors involved are

1. N-methyl-D-aspartate (NMDA) receptor (main)
2. alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)
3. metabotropic glutamate receptors. Activation of these receptors leads to membrane depolarization and increased calcium influx.

Another effect of NMDA receptor activation is the production of nitric oxide. Hypoxia leads onto the stimulation of the nitric oxide synthase, which results in the elevated levels of nitric oxide.

Nitric oxide is plays a significant role in the signaling in the human body at the normal physiological range . As an example, endothelial nitric oxide synthase (eNOS) leads to the production of low levels of nitric oxide that cause vasodilation and increase blood flow. However, neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) result in larger amounts of nitric oxide that may lead to brain injury.

Nitric oxide is a free radical and reacts directly with cellular components to damage them. Nitric oxide can also react with another free radical, superoxide, to produce the highly reactive peroxynitrite. Peroxynitrite causes single strand breaks in DNA. This results in the activation of DNA repair enzymes, which consume vital energy needed for other processes. DNA damage also may activate the process of apoptosis, leading to cell death.

The production of reactive oxygen species, a normal byproduct of oxidative metabolism, is also increased during ischemia. Like nitric oxide, they can react with and damage cellular components. Injury to the plasma membrane of a cell can lead to the inability to control ion flux, resulting in

mitochondrial failure. Reactive oxygen species, as well as calcium influx and other factors, can also permeabilize the mitochondrial membrane. This leads to metabolic failure as well as the release of initiators of apoptosis and DNA damage.

Metabolic failure results in the depletion of cellular ATP levels. ATP is required for nuclear condensation and DNA degradation in the final stages of apoptosis. In the absence of ATP, cell death occurs by necrosis rather than apoptosis. The release of byproducts from cellular damage and death by necrosis activates components of the inflammatory pathway. The role that inflammation plays during ischemia is mixed, having both positive and negative effects.

On way the surrounding inflammation results in proliferation of blood vessels and thereby increasing the blood flow to affected region.this will deliver more oxygen and glucose to the tissue . On the other hand, increased blood flow may also deliver more calcium to the area where the damage will be more.

Inflammation also results in the migration of activated leukocytes to damaged tissue. Although these leukocytes may remove damaged and necrotic tissue, they also release cytokines to attract additional inflammatory cells. Under severe inflammatory conditions, these cytokines can accumulate

to toxic levels. The cell death can occur by two ways: either by the apoptosis, or by the necrosis.

The pattern of cell death after cerebral ischemia depends on the nature of the insult to cerebral tissue. In global cerebral ischemia, such as occurs after cardiac arrest and resuscitation or transient severe systemic hypotension, the entire brain is exposed to ischemia. Formation of infarct is not immediate, but rather occurs after a delay of 12 hours to several days. Cell death is limited to those regions of the brain that are particularly susceptible to ischemic damage, such as the CA1 and CA4 regions of the hippocampus, the striatum, and cortical layers two and five. Cell death in these regions occurs primarily by apoptosis.

Focal cerebral ischemia is a more common pattern than global ischemia in human stroke. In animal models of focal ischemia, changes in cell morphology are visible microscopically as early as two to three hours after the insult, and the infarct develops rapidly over a period of 6 to 24 hours. Cell death occurs by necrosis in the core, with apoptotic cells located on the periphery.

In addition to the type of insult, the duration of ischemia also affects the pattern by which cell death occurs. Longer ischemic insults produce

greater damage to cerebral tissue, resulting in an increased proportion of necrosis and decreased proportion of apoptosis.

There have been few studies of apoptosis in the brain following stroke in human patients. However, accumulating evidence suggests that apoptosis is involved, as illustrated by the following observations[29,30]:

- In a neuropathology study that compared specimens from 27 patients who had cerebral infarction with specimens from rat brains subjected to experimental transient forebrain ischemia, the patterns of cell death were similar in human and animal brain tissue and included both morphologic and histochemical findings typical of apoptosis . In the human stroke specimens, apoptosis was apparent during the subacute stage, but was not seen in acute or chronic stages.

- In another neuropathology report that compared 13 cases of fatal ischemic stroke with three patients who died of non-neurologic causes, histochemical and morphologic changes indicative of apoptosis were seen in cells throughout the brain of both patients and controls . The morphologic changes were more advanced in the peri-infarct region and infarct core of the patients with stroke. Apoptotic cells were located primarily within the peri-infarct region, consisting of up to 26

percent of all cells. Increased ischemic damage and neuronal necrosis was associated with a decrease in the percentage of apoptotic cells.

The deciding factor in determining whether cells undergo necrosis or apoptosis seems to be the level of energy available in the form of ATP, which is required for formation of the apoptosome. Apoptosis is unable to proceed in its absence.

When energy levels are limiting, cell death therefore occurs by necrosis rather than apoptosis. The role of ATP in the mechanism of cell death has been investigated primarily using cell culture models. Cultured neurons depend on the presence of serum in the culture medium for survival. If the serum is removed, the cells die by necrosis. In serum-free media with added glucose, however, the cells die by apoptosis.

ATP levels are decreased in acute stroke because of decreased blood supply. Glucose metabolism is decreased by about 50 percent in both global and focal ischemia models of stroke. As a consequence, ATP levels may fall to 10 percent of normal in global models or 25 percent in the infarct core in focal ischemia models. ATP levels in the penumbra, however, only drop to 50 percent to 70 percent of normal.

ATP levels in the brain may also be decreased by mitochondrial damage or failure, activity of DNA repair enzymes, such as PARP, and neuronal depolarization related to glutamate excitotoxicity. In stroke, in the central area of infarction where the ATP level is least necrosis takes place whereas in the penumbra ATP levels will be slightly more than the central area and thereby apoptosis occurs. Hence the duration of ischemia directly related to the area of necrosis.

Loss of brain structural integrity

Occlusion of the blood supply to brain leads on to the disturbance in the integrity of blood vessels. This is mediated by the action of various substances like matrix metalloproteases (MMP), which destroy laminins, collagens in the blood vessels. The breach in the blood-brain-barrier will result in the formation of the cerebral edema resulting in raise in intra cranial hypertension. This will also results in the ischemic infarct developing complications like hemorrhagic transformation .

Cerebral edema :

Cerebral edema complicating stroke can cause secondary damage by several mechanisms, including increased intracranial pressure, which may decrease cerebral blood flow, and mass effect causing displacement of brain

tissue from one compartment to another (ie, herniation), a process that can be life-threatening.

Two types of cerebral edema can occur as a consequence of ischemic stroke

1. **CYTOTOXIC EDEMA -** The failure in the energy dependent pumping system (of Sodium &Calcium) in the cell fails as a result of ischemia. This will leads on to the accumulation of water inside the cells, causing swelling of the neurons, and hence the brain.

2. **VASOGENIC EDEMA** – The breakdown of the blood brain barrier will results in the leakage of osmatically active proteinous substance from the intravascular region into the interstitial spaces of the brain, leading on to raised extracellular fluid volume.

About 10 percent of ischemic strokes may be massive because of the presence of space-occupying cerebral edema that may be severe enough to produce elevated intracranial pressure and brain herniation.

CLINICAL FEATURES OF ISCHEMIC BASED

ON ARTERIAL TERRITORY INVOLVEMENT

Acute stroke syndromes according to vascular territory and mechanism

Artery involved	Syndrome	Pathophysiology
Anterior cerebral artery	Motor and/or sensory deficit (leg >> face, arm) Grasp, sucking reflexes Abulia, paratonic rigidity, gait apraxia	Embolic > atherothrombotic
Middle cerebral artery	Dominant hemisphere: aphasia, motor and sensory deficit (face, arm > leg > foot), may be complete hemiplegia if internal capsule involved, homonymous hemianopia Non-dominant hemisphere: neglect, anosognosia, motor and sensory deficit (face, arm > leg > foot), homonymous hemianopia	Embolic > atherothrombotic
Posterior cerebral artery	Homonymous hemianopia; alexia without agraphia (dominant hemisphere); visual hallucinations, visual perseverations (calcarine cortex); sensory loss, choreoathetosis, spontaneous pain (thalamus); III nerve palsy, paresis of vertical eye movement, motor deficit (cerebral peduncle, midbrain)	Embolic > atherothrombotic
Penetrating vessels	Pure motor hemiparesis (classic lacunar syndromes) Pure sensory deficit Pure sensory-motor deficit Hemiparesis, homolateral ataxia Dysarthria/clumsy hand	Small artery (lacunar) infarct
Vertebrobasilar	Cranial nerve palsies Crossed sensory deficits Diplopia, dizziness, nausea, vomiting, dysarthria, dysphagia, hiccup Limb and gait ataxia Motory deficit Coma Bilateral signs suggest basilar artery disease	Embolic = atherothrombotic
Internal carotid artery	Progressive or stuttering onset of MCA syndrome, occasionally ACA syndrome as well if insufficient collateral flow	Atherothrombotic > embolic

WATER SHED INFARCTS:

It occur in the border region between two arterial territory. These infarct are common during or after the surgery, severe arterial hypotension after cardiac arrest, prolonged hypoxemia, bilateral severe carotid artery diseases.

Ischemia in the border zone of the ACA, MCA & PCA manifest in the form of bilateral parieto-occipital infarcts with clinical features of visual disturbances, optic ataxia, cortical blindness and difficulty in predicting the size, distance and movement.

Unilateral severe arterial occlusion or stenosis will leads to unilateral watershed infarct when these is some degree of hemodynamic failure in these patients. This can also occur in the situation of microembolism or the hyperviscosity states.

Ischemia between ACA & MCA region results in bilateral upper limb cortical sensorimotor impairment (man-in-barrel), impaired saccadic eye movements due to involvement of frontal eye fields.

MCA & PCA territory involvement results in bilateral parieto temporal infarction with cortical blindness, defect in the verbal & the non verbal material. dyslexia, dyscalculia, dysgraphia.

Watershed infarct can also occur in the regions of PICA, AICA & SCA., also involving internal watershed region in the centrum semi ovale near to & slightly above the body of lateral ventricles.

MANAGEMENT OF ISCHEMIC STROKE:

A) Initial evaluation:

1. Management of airway, breathing, circulation
2. Neurological examination to look for neurological deficit, and to localize into the arterial territory.
3. Rule out possibility of stroke mimics – like hypoglycemia, hypertensive encephalopathy, seizures, etc.
4. Secondary assessment of the neurological deficit and possible risk factors
5. Etiology of the stroke to be assessed for early secondary prevention.

B) History taking & examination:

1. Time of onset of stroke – time when the patient was last seen to be symptom free.
2. Circumstances around the development of the symptoms – whether at rest or during exertion.
3. History suggestive of other potential causes of the symptom.
4. History of medications – anticoagulants, anti-platelets agents

5. Evaluate for the risk factors like cardiac disease, arteriosclerosis, drug abuse, migraine, seizure, pregnancy.
6. Assessment of airway, breathing, circulation – including pulse oximetry, blood glucose, body temperatue
7. Looking for signs of trauma, carotid bruits, seizure activity (contusions, tongue bite), congestive cardiac failure.
8. Cardiovascular examination to search for valvular heart disesases, irregular rhythm, and associated heart diseases.
9. Skin examination to detect coagulopathy, platetlet disorders, etc
10. Grading of severity of stroke by using NIHSS scale, as this will important prognostic information.

C) INVESTIGATIONS:

1. Basic work-up including complete blood count, blood urea nitrogen, creatinine, electrolyte, liver function test, bleeding time, clotting time, prothrombin time, partial thromboplastin time, blood glucose level, lipid profile, chest X ray, electrocardiogram, urine analysis.
2. Non contrast CT:

   This is the diagnostic brain imaging study in the initial stroke evaluation.[31]

   (A) Hyperacute infarct (<12 hours): in this stage, there will be early changes in the form of grey-white matter differentiation will be

lost, sulcus & sylvian fissure effacement & obscuration of the lentiform nucleus. Dense MCA sign- Horizontal part of the middle cerebral artery may appear hyperdense, even before the appearance of infarct.

(B) Subcute infarct (24-48 hours):

Wedge shaped area of decreased attenuation involving both the grey and with matter in a typical vascular territory. The initial mass effect then begins to decrease in 7-10 days.

(C) Chronic infarct:

Well delineated, focal areas of encephalmalacia appears in CT scans. Adjacent sulci become prominent and the ventricle on the ipsilateral side enlarges. Enhancement disappears after eight to ten weeks.

Scan negative infarct: early scans may be negative in 60% of cases [32] within12 hours of ictus, after 2 -3rd week after infarct (blooming).

3. MULTIMODAL CT:

i) Whole brain perfusion CT- identify the cerebral blood volume and areas of hypoattentuation representing the ischemic core.

ii) dynamic perfusion CT – provides absolute measures of cerebral blood flow, mean transit time and cerebral blood volume.

iii) helical angiography – non invasive method to assess the vasculature of both the intra-cranially and extra- cranially and identify the stenosis or occlusion of the vessels.

4. Magnetic resonance imaging (MRI):
    - Superior in detecting ischemia, when compared with CT.
    - In acute infarct, DWI is highly sensitive in the first few hours after infarction. The diffusion restriction in acute infarct will appears as high intensity in DWI images with low ADC signal and appears dark, and during the initial stages T2 weighted images are normal.
5. Multimodal MRI:
    - Diffusion weighted MRI (DWI) – identify ischemic regions within minutes of symptom onset and early identification of lesion size, site & age.

The infarct volume on DWI is calculated by using the product of “a”, “b”, “c” divided by 2, where the “a’ stands for the maximum length of the infarct, “b” stands for maximum breadth of the infarct, “c” stands height of infarct seen in the diffusion weighted images

- Perfusion weighted MRI (PWI) – provides relative measures of cerebral hemodynamics. The ischemic penumbra is approximated on MRI as region of perfusion change without a corresponding diffusion abnormality (diffusion perfusion mismatch)[33]

6. MRI angiography:

   Delineates blood flow & vascular lesions, including atheromatous plaques in the carotid and vertebrabasiliar systems. Identify the larger blood vessel abnormality better than that of the distal lesions.

7. Other brain imaging:– includes oxygen-15 Positron emission tomography (PET); Xenon enhanced CT brain; Single photon emission computed tomography (SPECT) identifies thresholds of reversible ischemia; transcranial Doppler sonography for evaluation of the blood flow velocity and patency of the main intracranial arteries.

8. Duplex Doppler ultrasonography - for detection of the carotid of the atheromatous plaques and obstruction of the carotid artery.

9. Echocardiography to assess the potential causes of TIA or evolving stroke.[34]

TREATMENT:

Treatment Of Acute Ischemic Stroke:

(A) GENERAL SUPPORTIVE CARE

a) Hypoxia worsens the outcome from the acute ischemic stroke. The airway protection and maintenance of the saturation is vital. Target oxygen saturation level is of 95%.

b) Fever-Increased metabolism, increased release of neurotransmitters, and increased free radical production is the possible mechanism responsible for worsening of the stroke by the fever.Antipyretic medications and cooling devices are advised measures to reduce fever.[35]

Hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury.

c) Arterial hypertension:

The increase in BP can be due the stress caused by ischemic event, distended bladder, prior hypertension, as result of hypoxia, or raised intracranial pressure. Aggressive control of BP in all cases can be detrimental, as the raise in blood pressure can be a result of protective auto regulatory mechanism.

Indications for reduction in blood pressure in ischemic stroke – when systolic BP > 220 mmHg, diastolic BP > 120 mmHg.[36]Or else when the raise in BP is associated with symptoms of heart failure, aortic dissection, acute coronary syndrome, hypertensive encephalopathy, renal failure. When patient is taken for IV thrombolytic therapy, the target BP is of < 185/110 mmHg prior to thrombolysis, and < 180/105 mmHg post thrombolysis.

d) Arterial Hypotension:

Correcting the state of hypovolemia with isotonic fluids, correcting the patient abnormal rhythm- to slow down the ventricular response in patient with AF with higher ventricular rate. If these effort fails, vasopressor should be considered.

e) Hypoglycemia:

Hypoglycemia can cause focal neurological signs, and hence the correction of the hypoglycemia is vital.

f) Diabetes mellitus - Hyperglycemia is associated with poor outcomes.[37]

B] REPERFUSION MEASURES:

(i) Thrombolytic therapy

The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg max; 10% as a bolus,then the remainder over 60 min) within 3 h of onset resulted in good

functionaloutcome though incidence of hemorrhage increased after thrombolysis Those withNIHSS score < 20responds well to the treatment.

In ECASS-II, IV rtPAwas not that much effective (in comparing with the placebo) in the final outcome of the stroke.

In the multicenter acute stroke trial Europe study group (MAST-E), streptokinase in the dose of 1.5 million units over one hour was associated with hemorrhagic transformation of ischemic infarct and hence not recommended. Intra-arterial thrombolysis has its role in cases of large artery occlusion, when intervention is done within six hours from the onset of the stroke . It is not FDA approved.

(ii) Anticoagulants

According to the Joint Guideline Statement from the AHA and AAN, urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended as it is associated with increased risk of bleeding complications[38]

(iii) Antiplatelet Agents

a) Aspirin

The International Stroke Trial (IST) showed a greater reduction in recurrence of the ischemic events by aspirin within the two weeks, but no

role in reducing the acute mortality . At 6 months, patients assigned aspirin had a significantly lower incidence of death and dependency.[39]

The Chinese Acute Stroke Trial (CAST) showed that aspirin reduced the mortality due to the stroke, but the role in reducing the long term mortality and morbidity is not improved.[40]

A combined result suggested that aspirin was beneficial in reducing recurrence of the ischemic stroke, death, or dependency.

b) Ticlopidine

In the ticlopidine aspirin stroke study, the risk of non fatal stroke or death from any cause at 3 years was lower in ticlopidine group as compared to aspirin group. The 3 year risk of fatal or non fatal risk was also lower .Thus it was concluded that ticlopidine was more effective than aspirin. The Canadian American ticlopidine study concluded that an exclusive benefit cannot be claimed for ticlopidine over aspirin in treating patients with stroke. [41]

c) Clopidogrel

It is a theinopyridine derivative which is a potent inhibitor of platelet aggregation caused by ADP. In a trial recent stroke/TIA patients were randomized to receive clopidogrel 75 mg/ day as compared with clopidogrel 75 mg/day with low dose aspirin 75 mg/day, showed no statistically

significant difference in outcome between the two treatment groups. Clopidogrel can be given to patients allergic to aspirin.[42]

(C) NEUROPROTECTIVE AGENTS

Hypothermia is probably the most powerful neuroprotectant. Various drugs have been tried like calcium channel antagonists (nicardipin, nimodipine), NMDA receptor agonist (selfolate, eliprodil), ICAM – I antibodies (Enlimomab), GABAnergic antagonists (Diazepam, Clomethiozole), glutamate antagonists (leleluzole), free radical scavengers (tirilazed, dihydrolipoate), lipid peroxidation inhibitors (Ebselen). Many of these drugs are in experimental stages and further studies are required before routine use .

(D) SURGICAL INTERVENTIONS

The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) single-arm trial investigated endovascular thrombectomy to restore patency of occluded intracranial vessels within 8 h of ischemic stroke symptoms. Recanalization of the target vessel occurred in 48% of treated patients and in 60% following use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favorable outcome. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) evaluated patients with symptomatic

stenosis of carotid arteries found a substantial benefits in patients with a stenosis of > 70%. [43]

(E) MANAGEMENT OF THE COMPLICATIONS:

(a) Raise in Increased Intracranial Pressure :

The goals of management of brain edema are to

- Reduce ICP
- Preserve perfusion to the brain
- Avoiding the herniation of the brain

Osmotic therapy (Mannitol) and hyperventilation have a vital role in reducing the ICP. The usage of the steroid in reducing the ICP secondary to stroke is not advisable. Decompressive surgery & evacuating the cerebellar infarcted areas causing the brain stem compression which leading to cause hydrocephalus are advisable.[44]

(b) Seizures

Usually on the first day of the stroke pateints are prone for developing seizures, which can be either focal or generalized seizures. The recurrent episodes are common in around twenty to eighty percentage of the cases. The role of prophylactic anti- epileptic therapy is not indicated

(c) Hemorrhagic Transformation

The use of all antithrombotic, but especially anticoagulants and thrombolytic agents, increases the likelihood of serious hemorrhagic transformation. The early use of aspirin also is associated with a small increase in the risk of clinically detectable hemorrhage.Management of patients with hemorrhagic infarction depends on the amount of bleeding and its symptoms.

RECOVERY FROM THE STROKE:

Usually most stoke recovery occurs in two to three months. 90% of recovery almost occurred within 2-3 years. Diabetes mellitus, prior stroke, cardiac diseases, ECG abnormality, prior functional dependence, severe motor deficits, sensory and visual deficit, loss of consciousness, cognitive deficit, incontinence are associated with poor outcome.

Recovery is better in the legs compared to the arm. The lack of measurable grip strength by 4 weeks following the stroke is a less favourable sign. Language function recovery is variable. The recovery is best for anomic aphasia, worst in the cases of global aphasia. Recovery from aphasia appears to occur independently of recovery from the hemiparesis. The recovery is better with usage of certain drugs like cholinergic, anticholinesterase, amphetamines, L-dopa, phenylephrine.

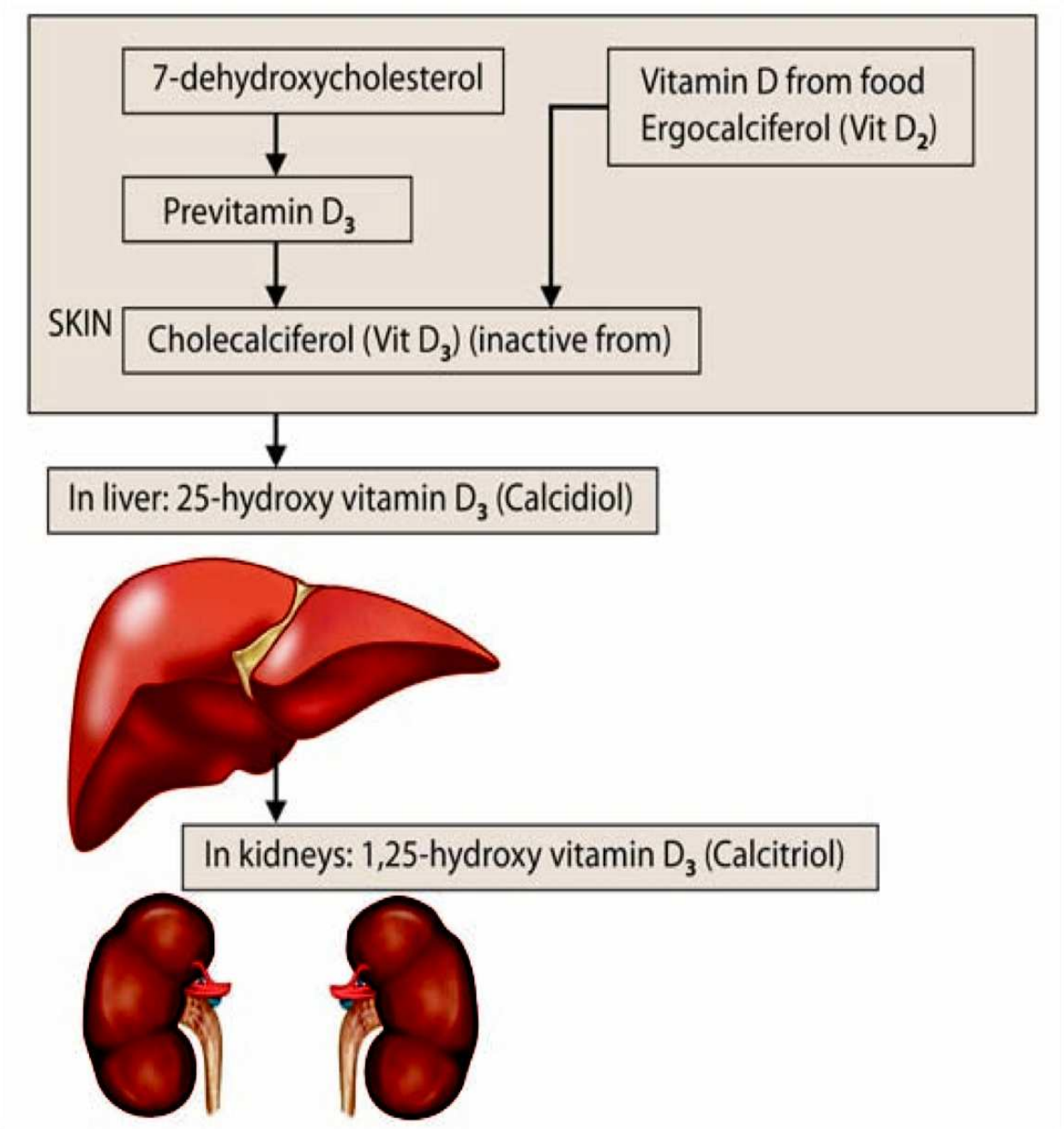
VITAMIN D:

McCollum, in the year 1922, discovered a new vitamin, which was the fourth vitamin identified at that time, and he named it as Vitamin D, representing the fourth letter of the alphabetical. It is the only vitamin in the body which can be synthesized in the human body itself. To be strict, vitamin D should be consider as a pro-hormone rather than a vitamin, as this can be synthesized in the body.

Vitamin D is essential in maintaining the normal calcium, phosphate levels in the blood. It is also required endocrine effect on calcium, thereby maintaining the normal mineralization of the bone. Other essential functions of Vitamin D include muscle contraction, nerve conduction, immune function, role in the inflammation in the form of cell proliferation and differentiation. Vitamin D insufficiency increase the risk for developing insulin resistance, Type-1 DM, hypertension, depression.

Calcitriol is the active form of the vitamin D. This active form of the vitamin is required for transcription of number of vitamin D dependent genes coding for protein regulating with calcium transport, bone matrix protein. Vitamin D synthesis start in the skin, wherein the sunlight exposure (UV B), converts the 7-dehydrocholestrol to vitamin D3 (also called as cholecalciferol). Thedietary source of vitamin D is mainly from the fish oil, egg yolk (vitamin D3), plant source. The plant source contains vitamin D2 (ergocalciferol).

SYNTHESIS OF VITAMIN - D

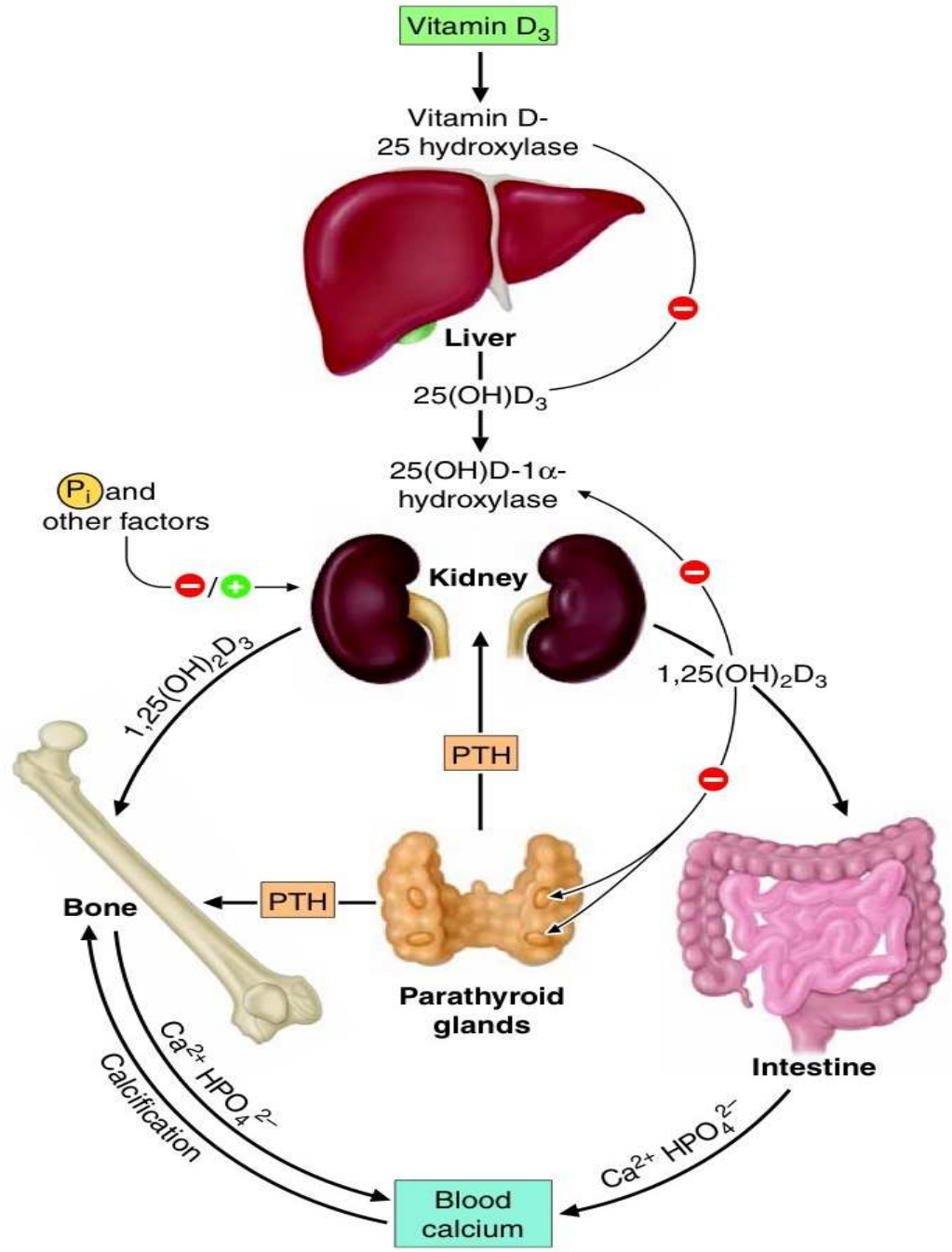


In circulation, Vitamin D is bounds to plasma protein mainly α-globulin, albumin. These two forms of inactive vitamin requires two step activation which takes place in the liver followed by kidney.The inactive forms are taken up by the liver, where, it undergoes 25-(OH) hydroxylation by the enzyme 25-hydroxylase, which is not tightly regulated, resulting in formation of 25-(OH) vitamin D3 and this forms the major storage component of vitamin-D.

Further activation takes place in the proximal convoluted tubules of the kidney, keratinocytes by the action of 1-hydroxylase, resulting in synthesis of 1,25–(OH)2 Vitamin D3. 1-hydroxylase is the rate limiting enzyme in the synthesis of active form of vit-D3, which is stimulated by parathormone, hypophosphatemia and is inhibited FGF 23, calcium.

The active vitamin undergoes entero-hepatic circulation, where it is dehydroxylated and the vitamin is converted into inactive form. The active form of vitamin D acts on the vitamin D receptor in the nucleus, resulting in transcription of genes necessary for calcium absorption and bone resorption.

Risk factors for Vitamin D deficiency includes old age, decreased sunlight exposure, dark skinned individual, obesity, fat malabsorption. Vitamin D deficiency can results due to decreased synthesis in the skin, decreased intake of Vitamin D, increased loss of vitamin D as a result of small bowel diseases, drug like barbiturates, phenytoin, rifampicin causing enzyme induction; isoniazid causing impaired 25-hydroxylation leading to rare causes of Vitamin D deficiency.



Schematic representation of the hormonal control loop for vitamin D metabolism and function. A reduction in the serum calcium below ~2.2 mmol/L (8.8 mg/dL) prompts a proportional increase in the secretion of parathyroid hormone (PTH) and so mobilizes additional calcium from the bone. PTH promotes the synthesis of $1,25(OH)_2D$ in the kidney, which in turn stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback.

The vitamin D deficiency prevalence in India is high, and according to studies upto 90% of indian are found to have hypovitaminosis, of which around forty to forty five percent of population have vitamin D deficiency. The ethnic differences in the vitamin levels been reported early with higher level of vitamin D deficiency in Indian population than that of the age and sex matched Chinese population.

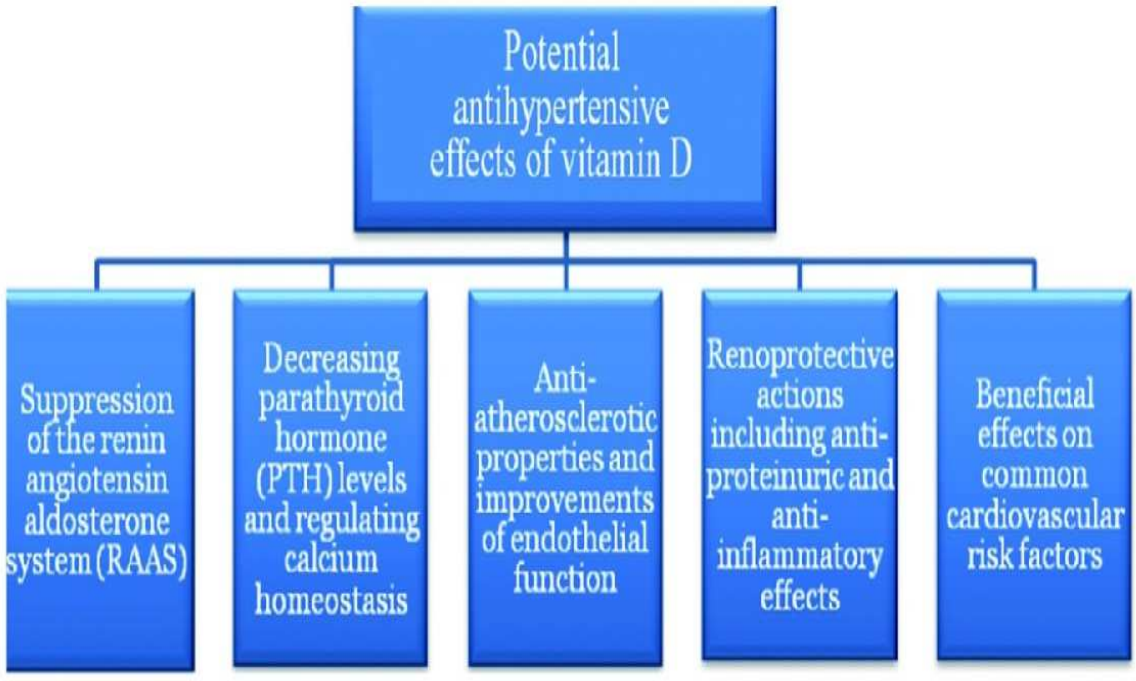
The clinical features include skeletal manifestations including rickets, osteomalacia, proximal muscle weakness,muscle soreness, bone pain, numbness, tingling sensation due to hypocalcemia. Decreased levels of 25-hydroxyvitamin D was found to be associated with cardiovascular diseases in form of atherosclerosis, coronary calcification.

Multiple recent studies found that decreased level of 25-hydroxyvitamin D is associated with carotid plaques and higher intimal media thickness valve, larger artery atherosclerosis, and smaller vessel diseases. Various studies revealed that vitamin D deficiency is identified as independent risk factor for the development of arterial hypertension, ischemic stroke (both thrombotic & embolic stroke). But the interventional studies involving vitamin D supplementation has no evidence to show that supplementation reduces the stroke incidence.

VITAMIN-D AND STROKE:

Vitamin D deficiency is identified as independent risk factor for development of stroke[49]. It is associated with severity of stroke, higher infarct volume, poor early functional recovery following stroke. Vitamin D deficiency increases stroke risk indirectly by causing hypertension, obesity. The decreased level of Vitamin D causes:

ACTIONS OF VITAMIN - D



(1) Increased Paratharmone levels – acute raise in PTH causes vasodilation, chronically increased PTH levels causes vasocontriction,; this high PTH levels are feature of Vitamin D deficiency, which leads to development of hypertension.

(2) Vitamin D has anti atherosclerotic, anti-inflammatory action. Decreased levels favour atherosclerosis.

(3) Anti-hypertensive effect of Vitamin D is by suppression of renin-angiotension-aldosterone, whish is lost in deficient state.

(4) Also, the renal protective effects & anti proteinuric effect is blunted in deficient state.

(5) Dysregulated inflammatory response, decreased Insulin like growth factor (IGF-1) leads to reduced neuro-protective actions[48]

(6) Reduced cognitive functions

Vitamin D deficiency diagnosis and management:

-The Vitamin D deficiency is assessed by measuring the level of 25-dihydroxyViatmin D in the serum. The is no specific concensus on the method of vitamin D assessment, and the level of deficient state. Vitamin D is assessed by chemiluminescent microparticle immunoassay (CMIA).[47]

(1) > 30ng/ml - considered normal[50]

(2) 10-30ng/ml - mild deficiency

(3) < 10ng/ml - severe deficiency

- Recommended daily amount for Vitamin D: is depends on the age.

  For people less than seventy year – 15 microgram per day or 600 IU/day. For people seventy year or above – 20 microgram per day or 800 IU/day .

- Vitamin D deficiency is treated with 50,000IU/week for around six to eight weeks, then followed by maintenance dose of 800IU/day.

- VitaminD toxicity occurs when daily consumption is more than 4000IU/day.

HYPERGLYCEMIA AND STROKE

Hyperglycemia is a commonly associated metabolic abnormality in patient with stroke. The presence of hyperglycemia in stroke on admission is associated with poor prognosis. Stroke associated with hyperglycemia is characterized by larger infarct volume with greater increases in infarct volume on subsequent days, with higher level of disability (neurological deficit), with higher mortality and morbidity.

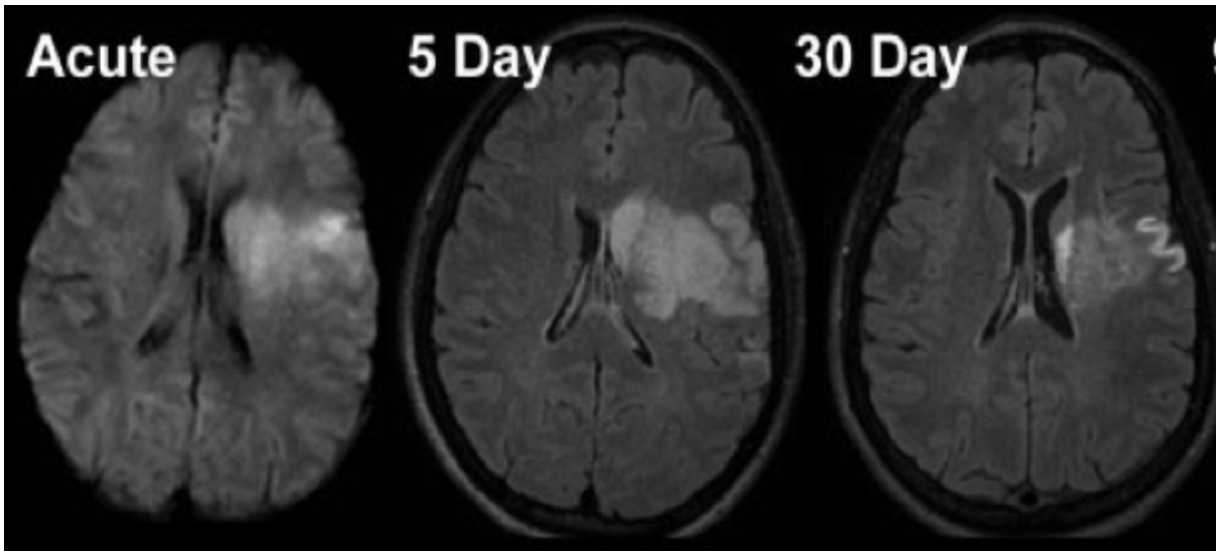
Stress hyperglycemia or in hospital hyperglycemia is present any blood glucose valve >140 mg/dl.[51] The frequency of stroke associated with hyperglycemia ranges from around 2/3 in all ischemic strokes, and around almost half of the patients with lacunar stroke.

The incidence of hyperglycemia during admission for stroke in a prior non-diabetic individual is 8-62% and in a known diabetic individual is 39% to 83%. This stress hyperglycemia is a state of pre-existing abnormal glucose metabolism, precipitated by stressful event in the form of stroke.

During follow up, about 27% to 37% of the patients were found to be have impaired glucose tolerance, with 1/3 of the remaining persons subsequently developed diabetes mellitus during next one year. On continuous monitoring of the glycemic status during the stay in the hospital will reveals that this early phase of hyperglycemia last for around 24 hours of

development of stroke, then reaches near the normoglycemic status, will later goes through a period of late hyperglycemia. The mortality is increased 18 fold in non-diabetic patients admitting with stroke and having hyperglycemia, wherein 3 fold increase in mortality rate in diabetic patient having hyperglycemia on admission.

According to recent studies, the ischemic stroke involving cortex & having stress hyperglycemia is associated with poor outcomes, where in cases of lacunar infarct this is correlation is not true, and this is associated with better outcome.



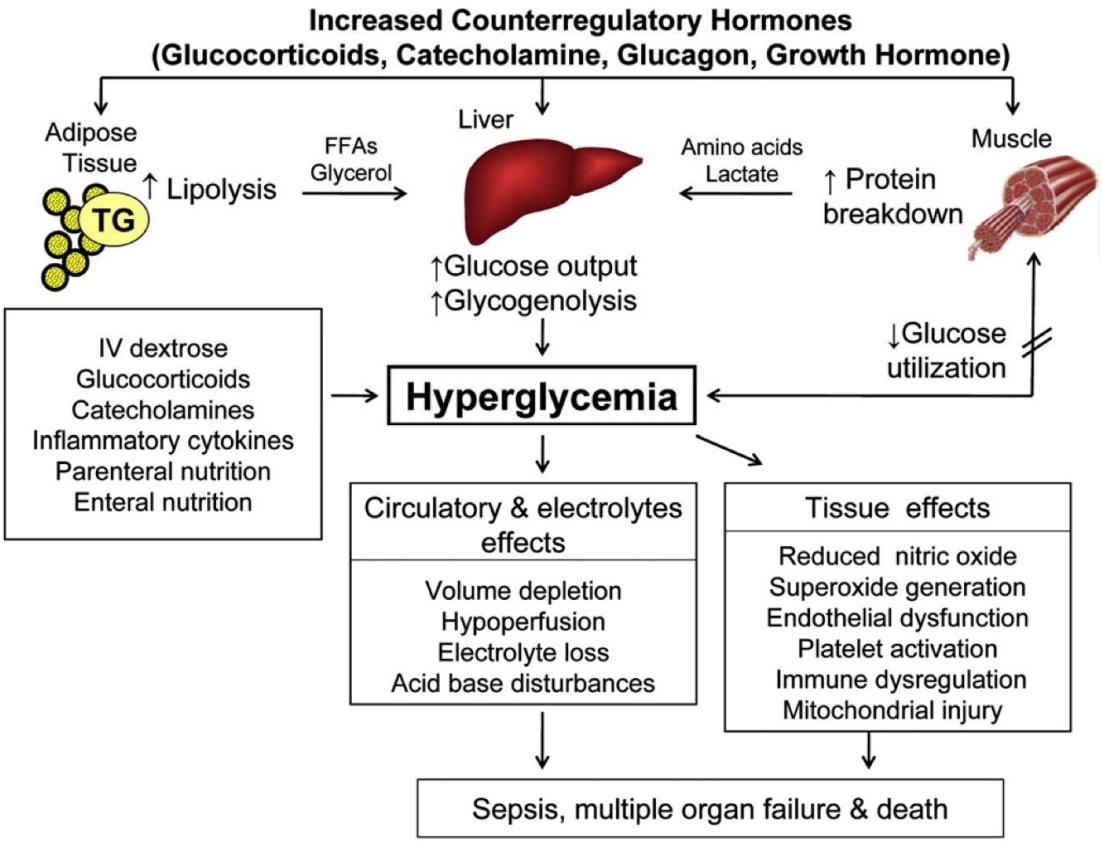
The infarct volume changes with as days progress with maximum volume is reached around 3-5th day after stroke[52], following which infarct volume decreases and attains stable volume around 90th day. The hyperglycemia is associated with higher infarct volume on admission, along with larger raise in the volume on subsequent days.

Stroke associated stress hyperglycemia are more prone for hemorrhagic transformation of the acute infarct, and also associated with poor outcomes with intravenous thrombolytics therapy; these patients develops hemorrhagic complications with thrombolytic therapy more frequently than that stroke patient with normoglycemic status.

Pathogenesis of stress hyperglycemia and stroke progression:

stroke causes a generalized stress reaction, which leads to stimulation of HPA axis. This leads to increased secretion of hormones like glucagon, corticosteroids, epinephrine, growth hormone resulting in hyperglycemia.

EFFECT OF HYPERGLYCEMIA



- The HPA axis stimulation is probably from the supra-pituitary level, mainly more when the insular cortex is affected in the stroke.
- Increased levels of stress hormone leads to glucogenolysis, decreased glucose uptake, with increased lipolysis, increased protein breakdown. These effect leads to hyperglycemia, which causes circulatory and tissue effects in the form of volume depletion, hypoperfusion, and electrolyte imbalance, with endothelial dysfunction leading to

vasoconstriction and platelet dysfunction, mitochondrial dysfunction. All these results in systemic hypoperfusion, infection, sepsis, multi organ failure and finally death.

- Hyperglycemia causes osmatic diuresis, volume depletion, hypotension, anaerobic metabolism leading to lactic acidosis. Excessive reactive oxygen species causes lipid peroxidation of the cell wall leading to cell wall lysis.
- Epinephrine excessive state causes decreased intake of glucose into the cell Leading to hyperglycemia and excessive insulin secreation and insulin resistance.
- Hyperglycemia causes damage to the blood brain barrier by reactive oxygen species formation and lipid peroxidation.
- Hyperglycemia triggers the glutamate mediated spreading of the depression waves of injury

HYPERGLYCEMIA AND AGGRAVATED CEREBRAL DAMAGE:

A) Impaired recanalization[53]:

- Increased thrombin/ Anti- thrombin complex
- Tissue factor pathway activation
- Decreased recombinant tissue plasminogen activator activity

B) Decreased reperfusion: hyperglycemia leading onto:-

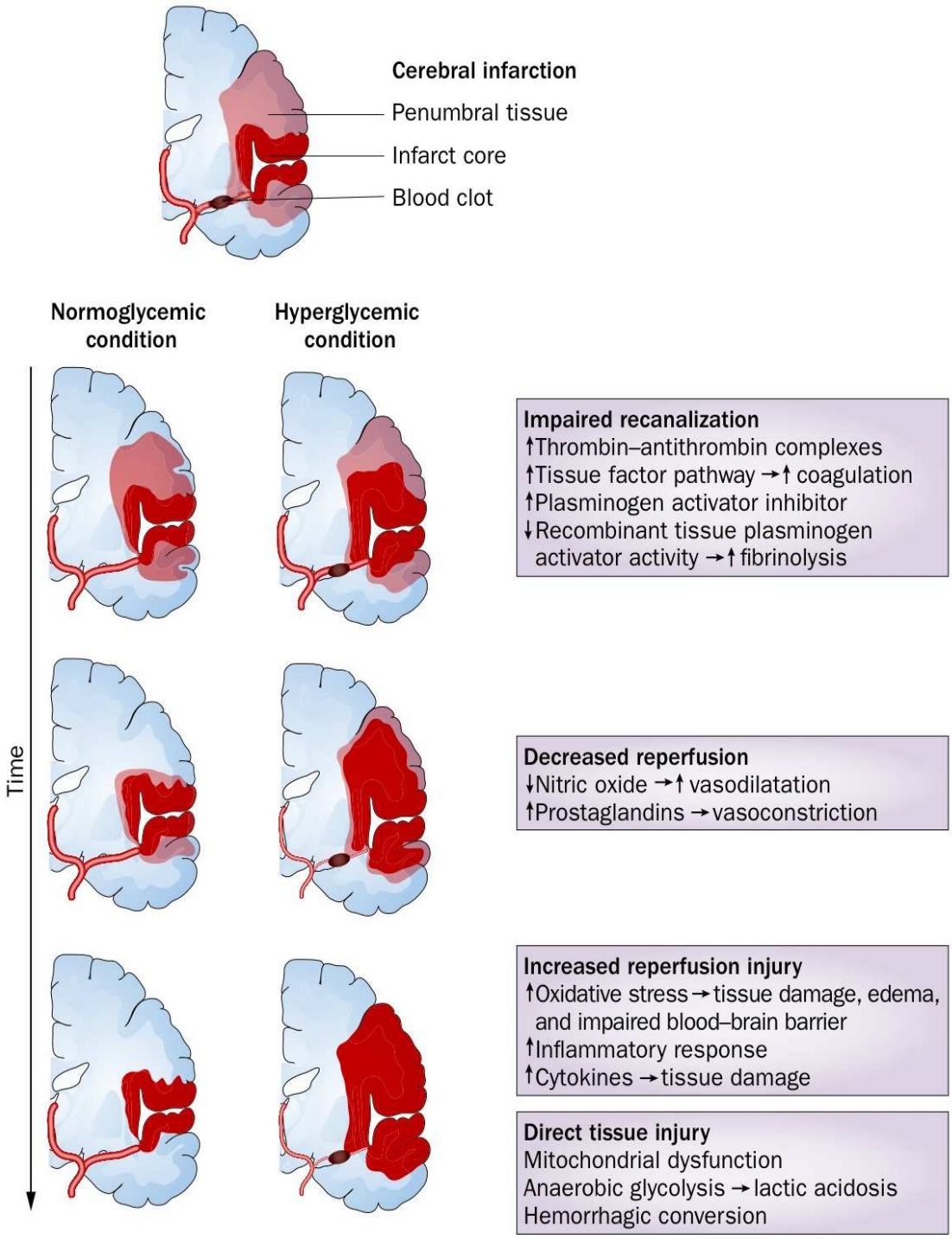
- Decreased Nitric oxide
- Increased prostaglandins

C) Direct tissue injury:

- Anaerobic glycolysis
- Mitochondrial dysfunction

D) Increased reperfusion injury:

- Oxidative stress
- Inflammatory response
- Cytokines causing tissue damage



| Schematic representation of infarct evolution over time. Hyperglycemia can have deleterious effects on various physiological processes associated with infarct evolution in patients with acute ischemic stroke.

NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

The Quantitative assessment of the stroke – related neurologic Deficit is assessed by using National Institute Of Health Stroke Scale (NIHSS). In this scale the neurological deficit is assessed byevaluating the motor functions, visual fields, ataxia, speech, language, cognition and sensory impairments. Score were given to calculate the deficit in each function individually and then combined totally for a total score. The higher the neurological functional loss, greater will be the NIHSS score. This scale provides a clinical tool for documentation of the neurological deficit. The scale also give information about the severity of the lesion, correlates well with the severity of the stroke, mortality and functional outcome. It serves for planning patient care and provides a common language for information exchange among health care providers. The NIHSS is a 15- item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual – field loss, extraocular movement, motor strength, ataxia, dysarthria and sensory loss. Scores less than five indicate mild neurological impairment, between five to fifteen means mild to moderately severe impairment, between fifteen to twenty five indicates severe impairment and scores greater than means very severe impairment. One additional point on the baseline decreased by 24% the likelihood of survival and excellent outcome at 7 days and by 17% at

3 months.The outcome is favourable when the bseline NIHSS score is low, with smaller vessel involvement.

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—alert
		1—drowsy
		2—obtunded
		3—coma/unresponsive
1B	Orientation questions (two)	0—answers both correctly
		1—answers one correctly
		2—answers neither correctly
1C	Response to commands (two)	0—performs both tasks correctly
		1—performs one task correctly
		2—performs neither
2	Gaze	0—normal horizontal movements
		1—partial gaze palsy
		2—complete gaze palsy
3	Visual fields	0—no visual field defect
		1—partial hemianopia
		2—complete hemianopia
		3—bilateral hemianopia
4	Facial movement	0—normal
		1—minor facial weakness
		2—partial facial weakness
		3—complete unilateral palsy
5	Motor function (arm)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 10 seconds
		3—no effort against gravity
		4—no movement
6	Motor function (leg)	0—no drift
	a. left	1—drift before 5 seconds

	b. right	2—falls before 5 seconds
		3—no effort against gravity
		4—no movement
7	Limb ataxia	0—no ataxia
		1—ataxia in one limb
		2—ataxia in two limbs
8	Sensory	0—no sensory loss
		1—mild sensory loss
		2—severe sensory loss
9	Language	0—normal
		1—mild aphasia
		2—severe aphasia
		3—mute or global aphasia
10	Articulation	0—normal
		1—mild dysarthria
		2—severe dysarthria
11	Extinction or inattention	0—absent
		1—mild (loss 1 sensory modality)
		2—severe (loss 2 modalities)

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

ETHICAL COMMITTEE APPROVAL:

Obtained.

STUDY DESIGN:

This study was conducted over a period of six months.

STUDY POPULTION:

Patients admitted with Acute ischemic stroke to the medical wards, Institute of Internal Medicine.

SAMPLE SIZE:

Fifty patients

TYPE OF STUDY:

Observational study

INCLUSION CRITERIA:

- Ischemic stroke patients admitting within 24 hours

EXCLUSION CRITERIA:

- History of previous ischemic stroke in the past.
- Any evidence of hemorrhage on CT BRAIN
- Massive infarct on imaging
- Patients selected for thrombolytic therapy.
- Transient ischemic attacks
- Cortical venous thrombosis

DATA COLLECTIONS AND METHODS

Informed consent obtained from each patients. Patients have their history taken according to the Questionnaire and subjected to clinical examination, NIHSS scale assessment.

On the time of the admission, the glycemic status of the patient is assessed by measuring the capillary blood glucose (CBG) levels, irrespective of the last meal status. Subsequently, during the stay in the hospital, blood glucose levels are monitored by using fasting and post prandial blood sugar levels.

During the admission, patients with ischemic stroke without evidence of hemorrhage in the CT Brain, was subjected to MRI Brain/MRA/MRV within 24 hours of onset of the neurological deficit. Then a repeat MRI Brain/MRA/MRV done on the 3-7th day. Then the volume of the ischemic stroke is assessed by using the Diffusion weighted images (DWI). The volume is calculated by using the product of “a”, “b”, “c” divided by 2, where the “a’ stands for the maximum length of the infarct, “b” stands for maximum breadth of the infarct, “c” stands height of infarct seen in the diffusion weighted images.

The volume of the infarct on the day one, volume of infarct on the day 3-7 is calculated, and the rise in the volume of infarct is measured by the difference between these two volume. These three volume are correlated with the capillary blood glucose (CBG) obtained during the admission.

The levels of Vitamin D [25-OH Vit D3 (total)] assessed by using chemi-luminescent immunoassay (CMIA), during the period of stay in the hospital. Then the patient classified based on vitamin D levels into normal (30-100 ng/ml) , insufficiency (10-30 ng/ml), deficiency (< 10 ng/ml).

All the data will be entered in the proforma (enclosed).

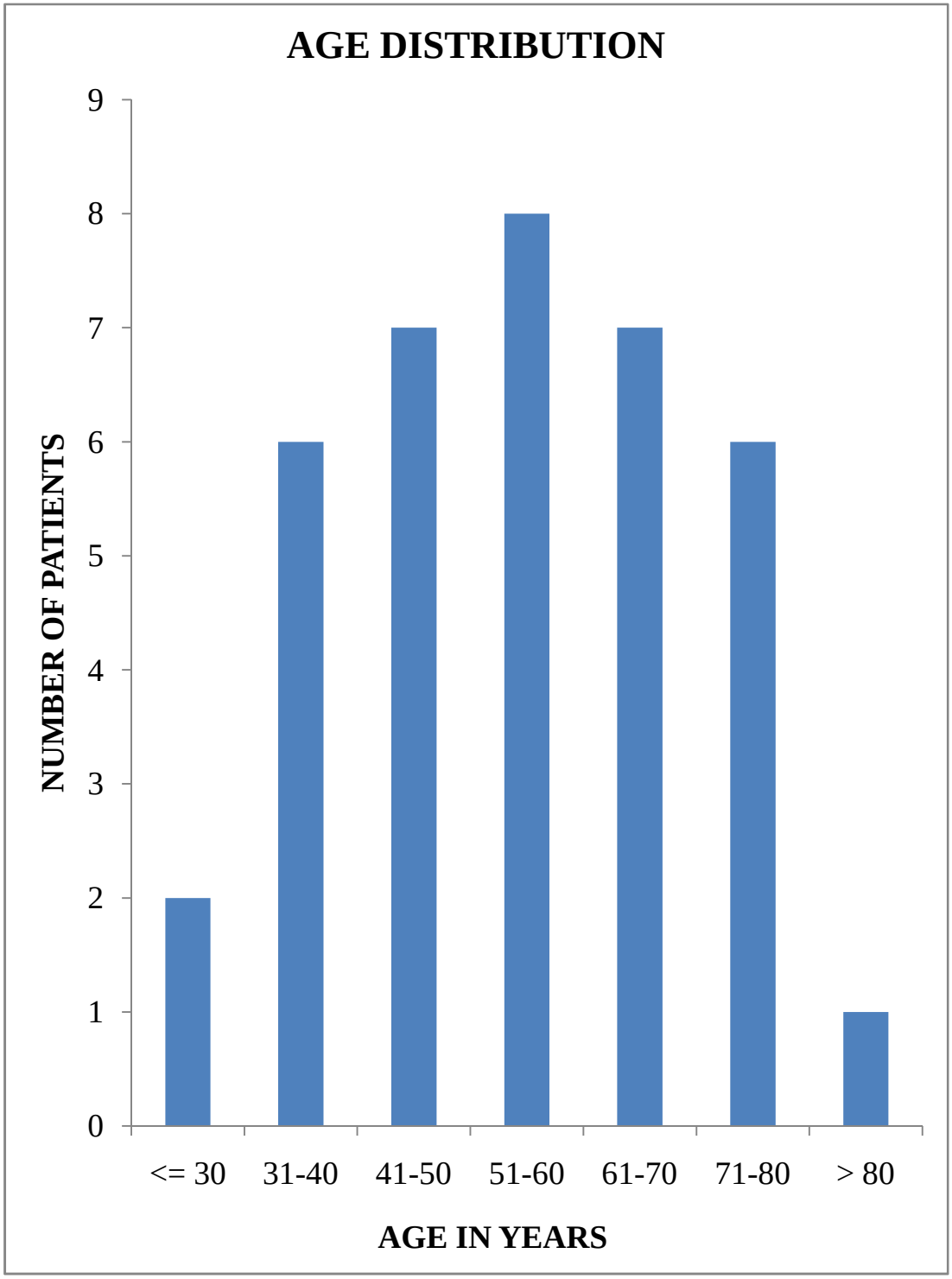
The data will be analysed by using SPSS package and ANOVA.

OBSERVATION AND RESULTS

OBSERVATION & RESULTS

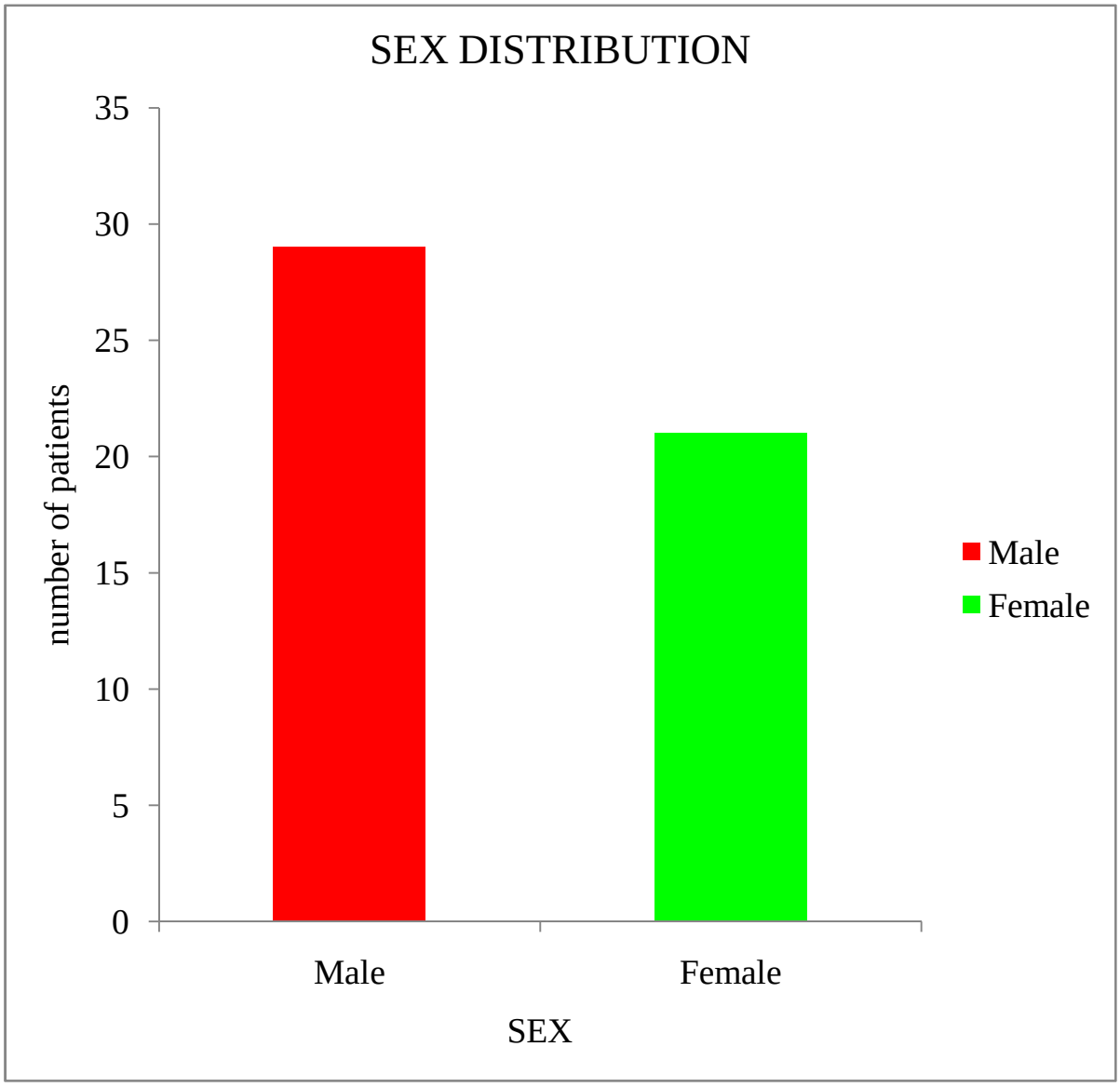
AGE DISTRIBUTION:

AGE (Years)	NUMBER OF PATIENTS	"p" valve
<= 30	3	0.733 (not significant)
31-40	8	
41-50	9	
51-60	11	
61-70	8	
71-80	8	
> 80	3	


AGE DISTRIBUTION
NUMBER OF PATIENTS
0
1
2
3
4
5
6
7
8
9
<= 30
31-40
41-50
51-60
61-70
71-80
> 80
AGE IN YEARS

SEX DISTRIBUTION:

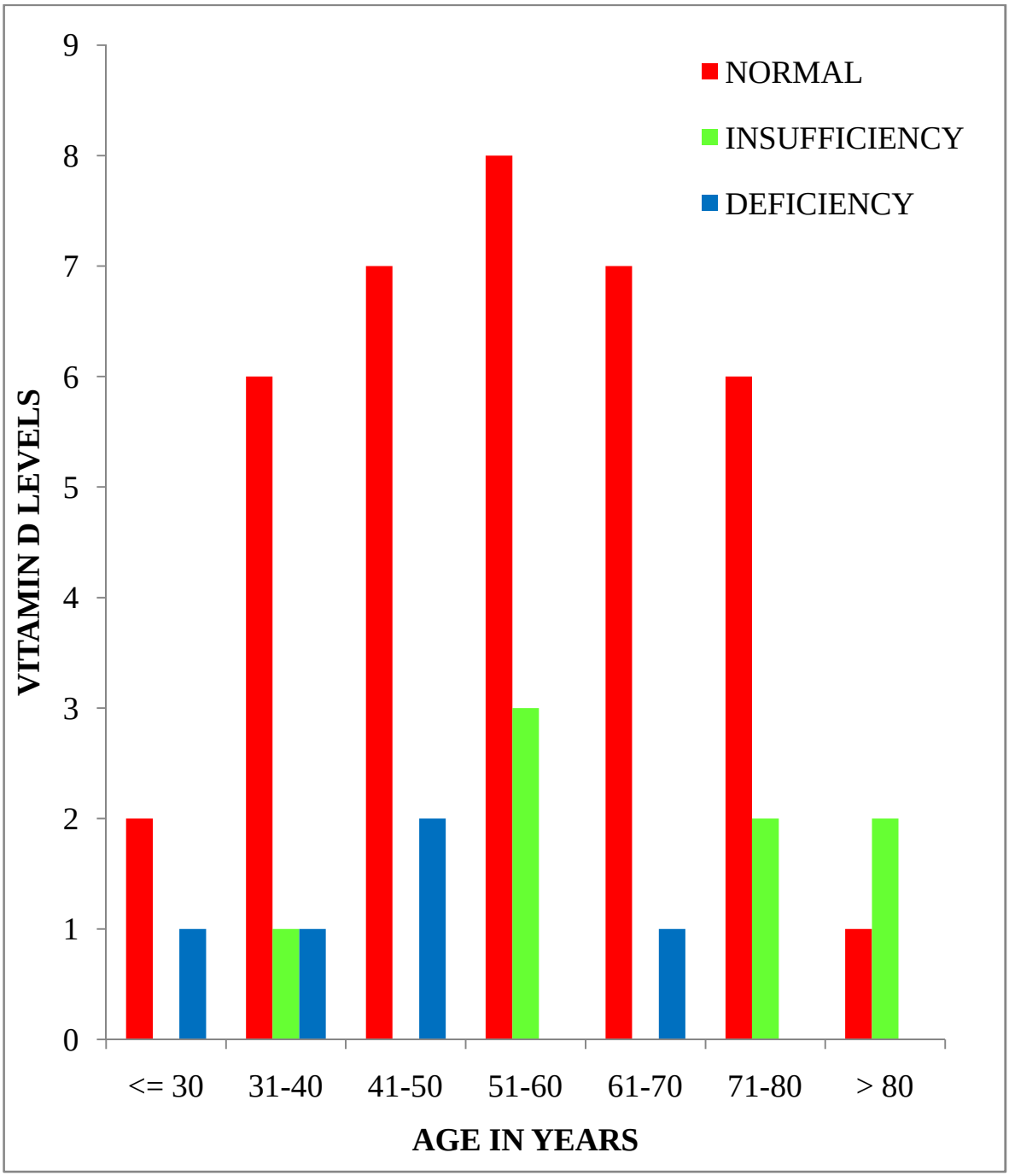
SEX	NUMBER OF PATIENTS	PERCENTAGE	"p" valve
Male	29	58	0.726 (not significant)
Female	21	42	


SEX DISTRIBUTION
35
30
25
20
15
10
5
0
number of patients
Male
Female
Male
Female
SEX

VITAMIN D LEVELS:

VITAMIN D LEVEL	NUMBER OF PATIENTS	P -VALVE
Normal	37	<0.001** (HIGHLY SIGNIFICANT)
Insufficiency	8	
Deficiency	5	

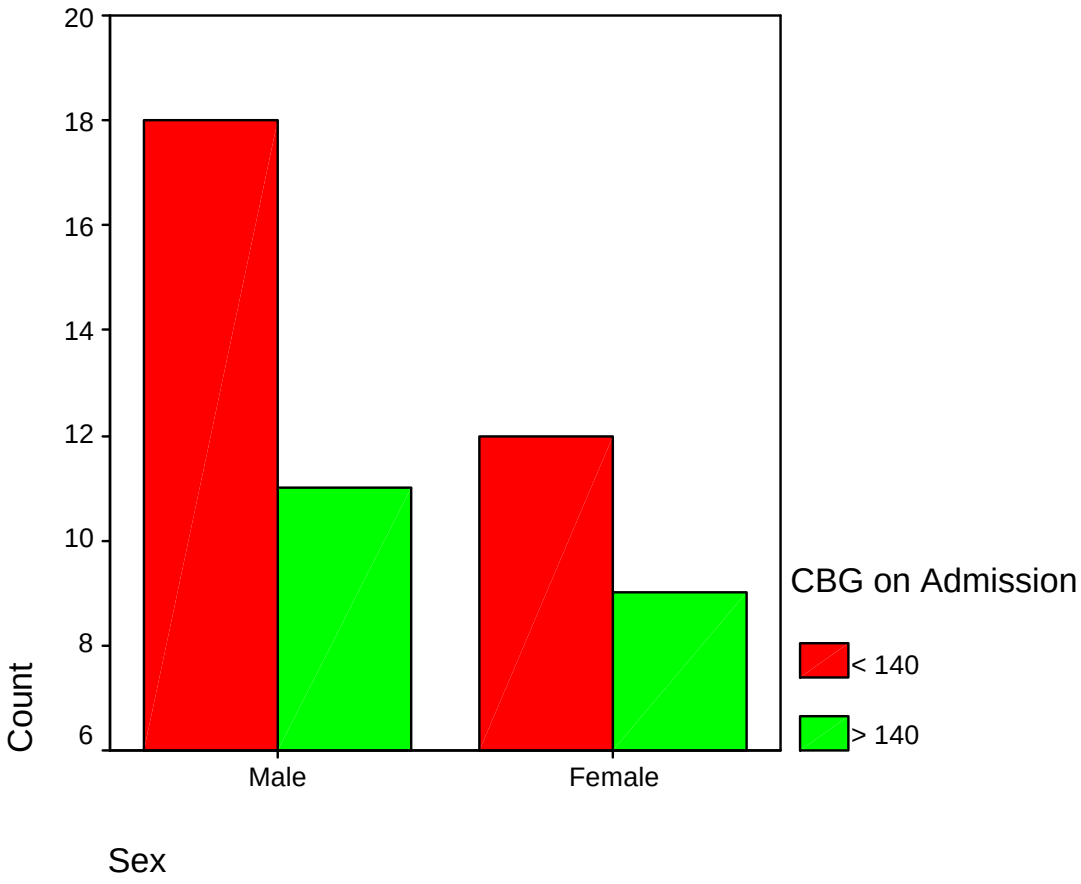
VITAMIN - D LEVELS IN DIFFERENT AGE GROUP:



GLYCEMIC STATUS ON ADMISSION:

	CBG < 140 mg/dl	CBG ≥140 mg/dl
MALE	**18**	**11**
FEMALE	**12**	**9**

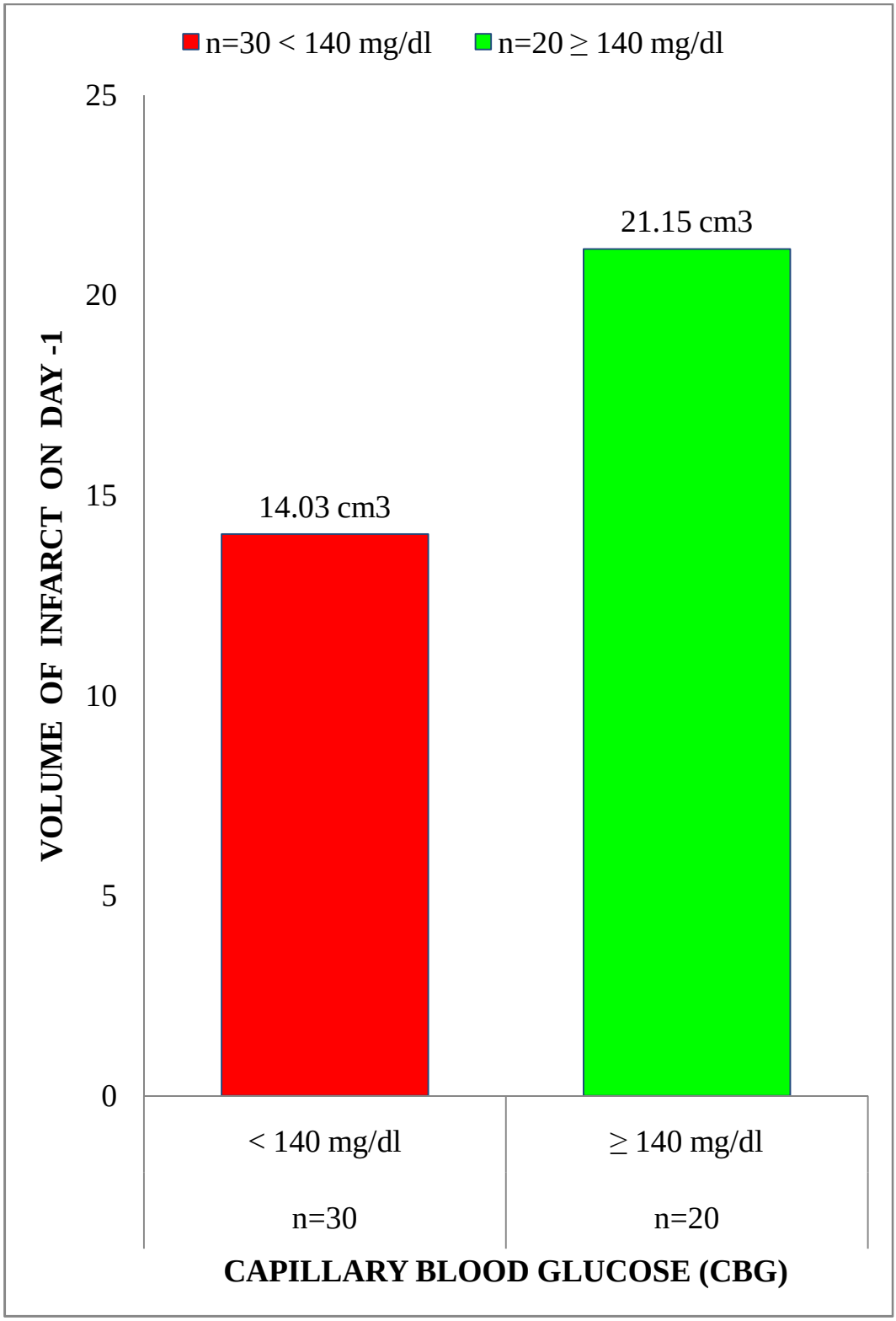
GLYCEMIC STATUS ON ADMISSION:



INFARCT VOLUME ON DAY 1 COMPARISON WITH CBG ON ADMISSION:

	CBG ON ADMISSION (mg/dl)	NUMBER OF PATIENTS	MEAN VOLUME (cm3)	STANDARD DEVIATION	P VALVE
INFARCT VOLUME IN < 24 HOURS	< 140	30	14.03	4.723	<0.001** (Highly Significant)
	≥ 140	20	21.15	6.02	

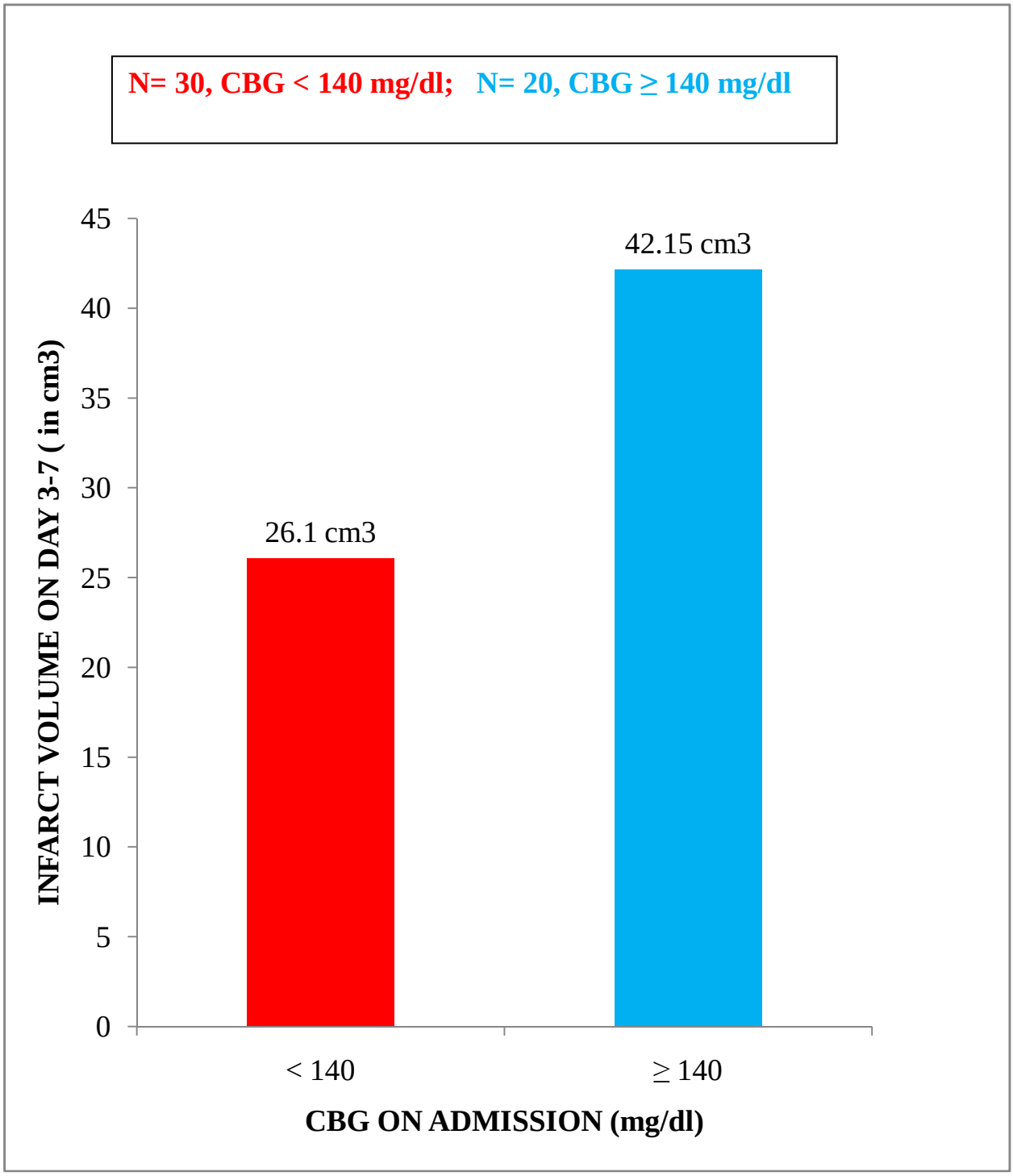
INFARCT VOLUME ON DAY 1 COMPARISON WITH CBG ON ADMISSION



INFARCT VOLUME ON DAY 3-7 COMPARISON WITH CBG ON ADMISSION:

	CBG on Admission (in mg/dl)	Number of patients	Mean volume (cm3)	Standard Deviation	P -valve
Infarct Volume on 3-7 Days	< 140	30	26.1	8.206	<0.001** (Highly Significant)
	≥ 140	20	42.15	9.138	

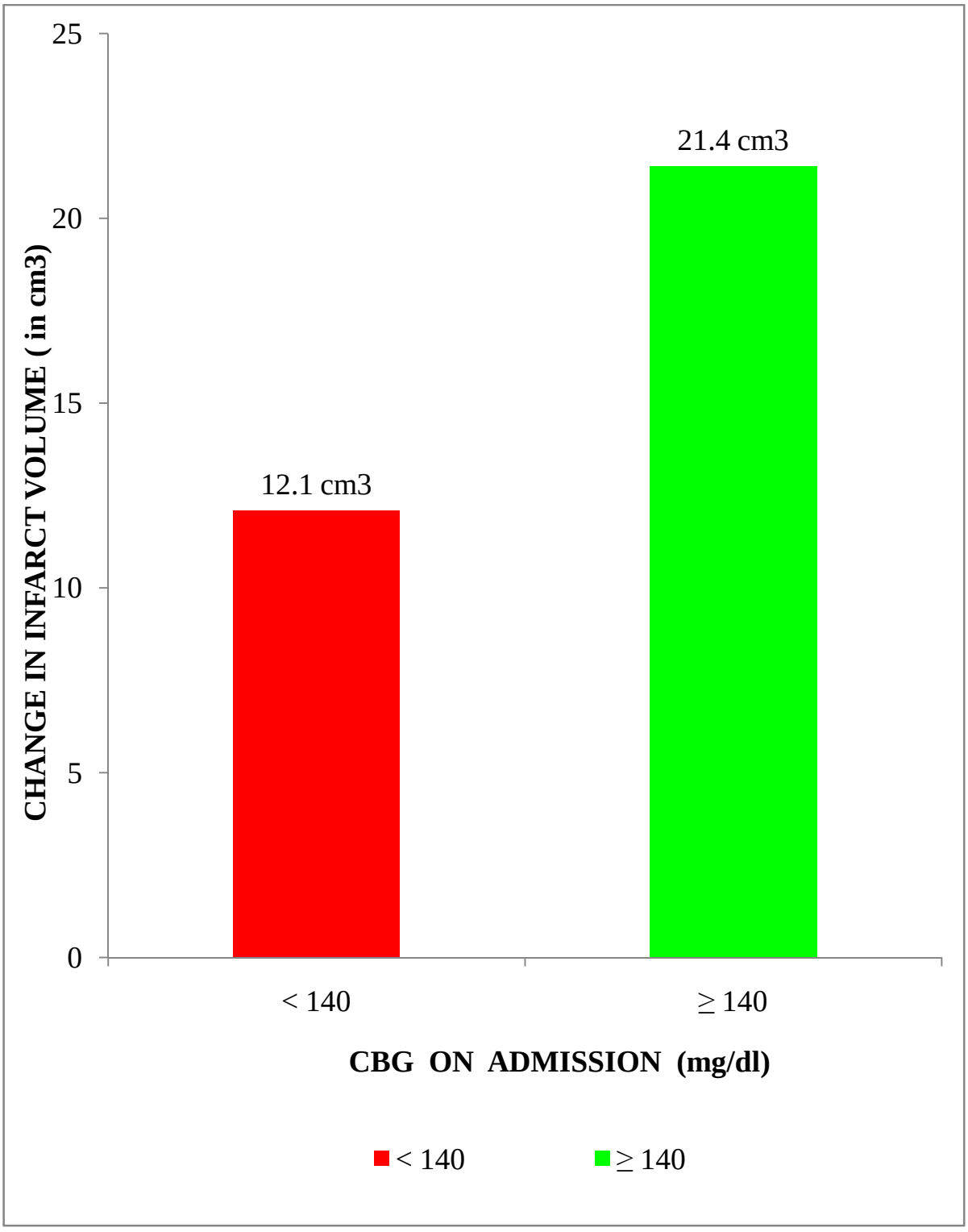
INFARCT VOLUME ON DAY 3-7 COMPARISON WITH CBG ON ADMISSION:



CHANGE IN INFARCT VOLUME COMPARISON WITH CBG ON ADMISSION:

	CBG ON ADMISSION (IN MG/DL)	NUMBER OF PATIENTS	MEAN VOLUME (CM3)	STANDARD DEVIATION	P -VALVE
CHANGE IN INFARCT VOLUME	< 140	30	12.1	4.559	<0.001** (Highly Significant)
	≥ 140	20	21.4	4.672	

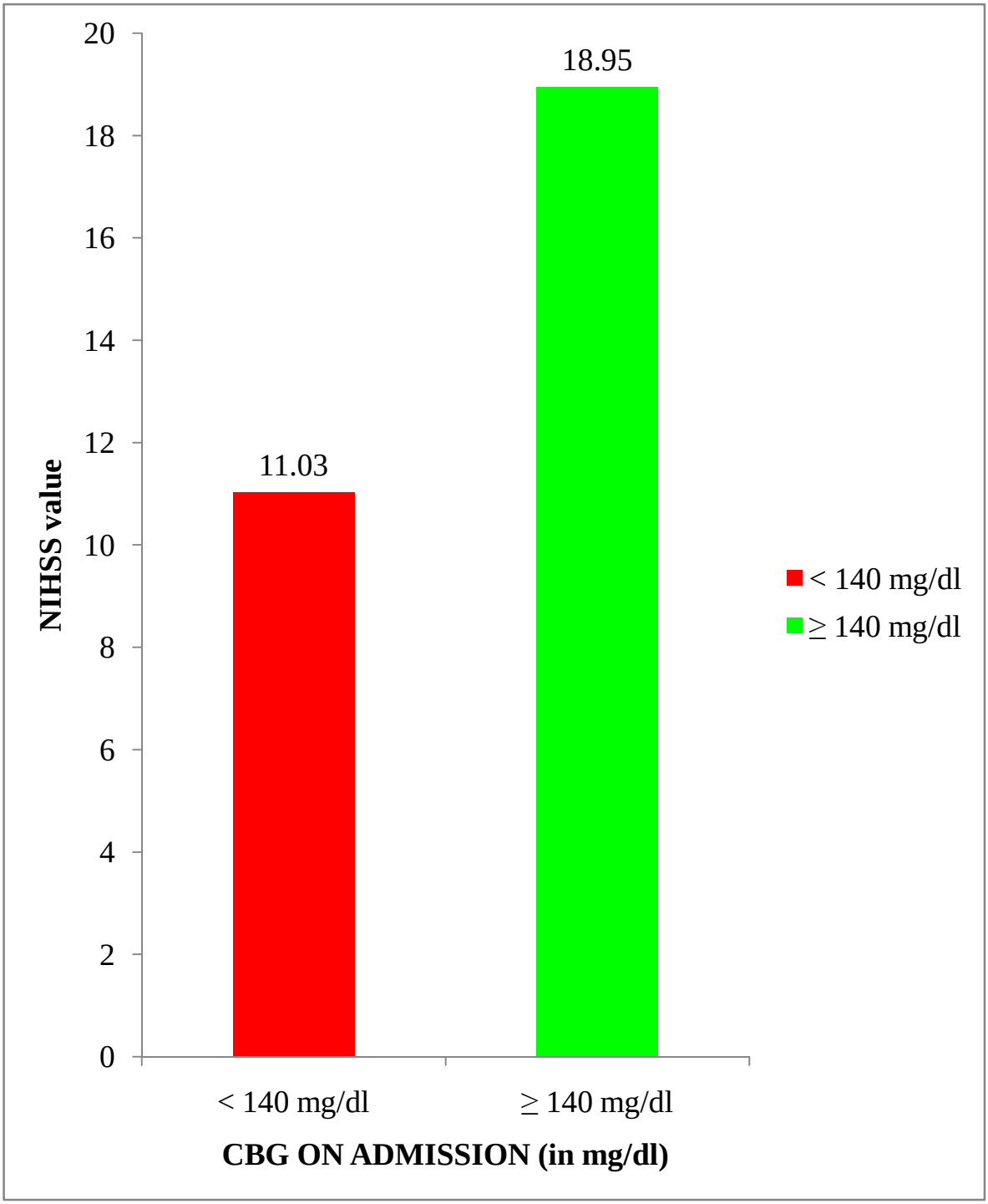
CHANGE IN INFARCT VOLUME COMPARISON WITH CBG ON ADMISSION



COMPARISON OF CBG ON ADMISSION WITH NIHSS:

	CBG ON ADMISSION (MG/DL)	**NUMBER OF PATIENTS**	**MEAN VOLUME (CM3)**	**STANDARD DEVIATION**	**P -VALVE**
NIHSS ON ADMISSION	< 140	30	11.03	3.243	<0.001** (Highly Significant)
	≥ 140	20	18.95	4.123	

COMPARISON OF CBG ON ADMISSION WITH NIHSS



RESULTS

AGE DISRIBUTION:

In our study among the ischemic stroke patients, the mean age of incidence is 55.86 years. In this, 6% were in the age group of less than 30 years, 16% were in the age group of 31 to 40 years, 18% were in the age group of 41 to 50 years, 22% were in the age group of 51 to 60 years, 16% were in the age group of 61 to 70 years, 16% were in the age group of 71 to 80 years, 6% were in the age group of > 80 years.

SEX DISTRIBUTION:

In our study among the ischemic stroke group, 58% were males, 42% were females.

VITAMIN D LEVELS IN THE ISCHEMIC STROKE PATIENTS:

In our study, 74% of the patients had normal levels of Vitamin D, 16% of the patients had Vitamin D insufficiency, and 10% of the patients had Vitamin D deficiency. Of the Vitamin D deficient individuals, 3 were males, and 2 were females. The correlation between ischemic stroke and Vitamin D deficiency is highly significant (< 0.001**).

GLYCEMIC STATUS ON ADMISSION:

In the study group, 60% were euglycemic on admission, and 40% were hyperglycemia on admission. Of the hyperglycemic patients, 11 patients were males and 9 patients were females.

CORRELATION BETWEEN GLYCEMIC STATUS ON ADMISSION AND INFARCT VOLUME:

In the study group, patient with euglycemic status on admission had a mean infarct volume of 14.03 cm^3 (in < 24 hours), 26.10 cm^3 (between 3^{th} to 7^{th} day after ischemic stroke), with a mean increase in the infarct volume of 12.10 cm^3.

In the patient with hyperglycemic status on admission had a mean infarct volume of 21.15 cm^3 (in < 24 hours), 42.15 cm^3 (between 3 to 7th day after ischemic stroke), with a mean increase in the infarct volume of 21.40 cm^3.

The infarct volume in < 24 hours, between 3^{rd} to 7^{th} days of the ischemic stroke and there progression is higher in hyperglycemic patients compared to that of the euglycemic patients, and these changes are highly significant (<0.001**)

CORRELATION BETWEEN GLYCEMIC STATUS AND NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS):

In the study group, the mean NIHSS score in euglycemic group is 11.03 cm^3, where is in the hyperglycemic group the mean NIHSS score is 18.95 cm^3.

DISCUSSION

DISCUSSION

- In a study by Bravata D. M. et al the mean age of the ischemic stroke is 73 ± 13 years. The mean age of male patients was 61.16 ± 14.88 years and the mean age of female patients was 57.33 ± 12.07yearsin Hyvarinen M et al study. In our study the mean age of occurrence is 55.86 years. The youngest patient was aged 15 years and the oldest was 85years. Maximum number of patients were in the age group of 51 – 60 years.

- Kushner et al in their study reported M : F ratio was 1.7 : 1.5. Hyvarinen M et alreported 55% men and 45% women in their study of 21,706 cases. In our study the incidence in male is 58% and in female 42%. The male: female ratio is 1.38: 1.

- In Jaydip Ray Chaudhuri et al studies, vitamin D deficiency had an independent association with the ischemic stroke. In our study also, the Vitamin D deficiency occurred in 10% of the cases, and insufficiency in 16% of the cases.

- In study done by Sarkar RN et al 38% had diabetics in their study of 450 patients. In this study, stress hyperglycemia was defined as admission blood glucose levels > 140 mg / dl. In our study the hyperglycemia cut-off is set as ≥ 140 mg/dl.

- Jhanghorbani M et al noted a stronger association between hyperglycemia and stroke in women than in men. In this study, 40% had hyperglycemia on admission, while remaining 60% are Euglycemic on admission. Of this, 37.93% of male are hyperglycemic, and 42.85% of female had hyperglycemia on admission. In this study, the random blood glucose on admission ranged from 90 mg/dl to 455 mg/dl. The range of blood glucose was 90 – 140 mg/ dl in the normoglycemic group. Most of the hyperglycemic patients had admission blood glucose between 140 – 220 mg/dl. Two patients had blood glucose > 400 mg/ dl on admission.

- Gentile NT et al noted that hyperglycemia was associated with higher admission NIHSS severity score. In our study, the mean NIHSS score is 18.95 in hyperglycemic patients and 11.03 in euglycemic patients.

- In studies by Tracey A Baird et al, hyperglycemia is associated with higher infarct on admission, and there progression is higher compared to that of the normoglycemic group. In our study group, patient with euglycemic status on admission had a mean infarct volume of 14.03 cm^3 (in < 24 hours), 26.10 cm^3 (between 3^{th} to 7^{th} day after ischemic stroke), with a mean increase in the infarct volume of 12.10 cm^3. In the patient with hyperglycemic status on admission had a mean infarct volume of 21.15 cm^3 (in < 24 hours), 42.15 cm^3 (between 3 to 7th day after ischemic stroke), with a mean increase in the infarct volume of 21.40 cm^3.

- This shows that admission hyperglycemia is associated with higher infarct volume & greater progression of the infarct when compared with that of the euglycemia on admission.

CONCLUSION

CONCLUSION

- According to our study, the hyperglycemia on admission is associated with greater infarct volume on admission, greater raise in the infarct volume in the subsequent days, with higher change in volume of infarct in the patient with hyperglycemia on admission, when compared that of the normoglycemia on admission.

- The vitamin D deficiency appears to be an independent correlation with the ischemic stroke.

LIMITATIONS

LIMITATION OF THE STUDY

- One limitation of this study is that the number of patients included in the study is less and so this study should be tested in studies involving larger number of patients.

- The management of the hyperglycemia and stroke per sec were not standardized.

- Extended follow up of the patients was not possible.

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ANNEXURES

“A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT”

PROFORMA:

Name : Patient ID No:
Age/Sex : Contact Address & Phone No:
Occupation :

Symptoms:

Past history:
*Diabetes mellitus:

*Hypertension

*Heart diseases

*Kidney disease

*Tuberculosis

*Other co morbid illnesses

Personal history:

*Smoking

*Alcoholism

General examination:
Vitals:
Pulse:
Blood Pressure:
Respiratory Rate:

Systemic examination:

CVS:
RS:
ABDOMEN:
CNS:
NIHSS scale:

Investigations:

CBC			LIPID PROFILE		
RBC			TOTAL CHL		mg/dl
TC	DC N	L	TGL		mg/dl
	E	B	HDL		
HB			LDL		
ESR					
PLATELET					
RFT			LFT		
Glucose		mg/dl	Total bilirubin		mg/dl
Urea		mg/dl	Direct bilirubin		mg/dl
Creatinine		mg/dl	SGOT		U/l
Na+		mEq/l	SGPT		U/l
K+		mEq/l	ALP		U/l
			Total protein		g/dl
			Albumin		g/dl

Vitamin D3:
Random Blood glucose On admission:

Chest X-ray:

ECG:
ECHO :

MULTIMODAL CT (OR) MRI BRAIN DWI
CAROTID AND VERTEBRAL DOPPLER:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.M.Balachandran,
Post Graduate, MD (General Medicine),
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600 003.

Dr.M.Balachandran,

The Institutional Ethics Committee has considered your request and approved your study titled **"A study on Vitamin-D level and glycemic status in acute ischemic stroke and their impact"** No.46072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandhini, M.D., Inst.of Pharmacology, MMC	: Member
5. Dr.G.Muralidharan, Director Incharge, Inst.of Surgery	: Member
6. Prof.Md.Ali, M.D., D.M., Prof & HOD of MGE, MMC	: Member
7. Prof.K.Ramadevi, Director i/c, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.Tito, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10.Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

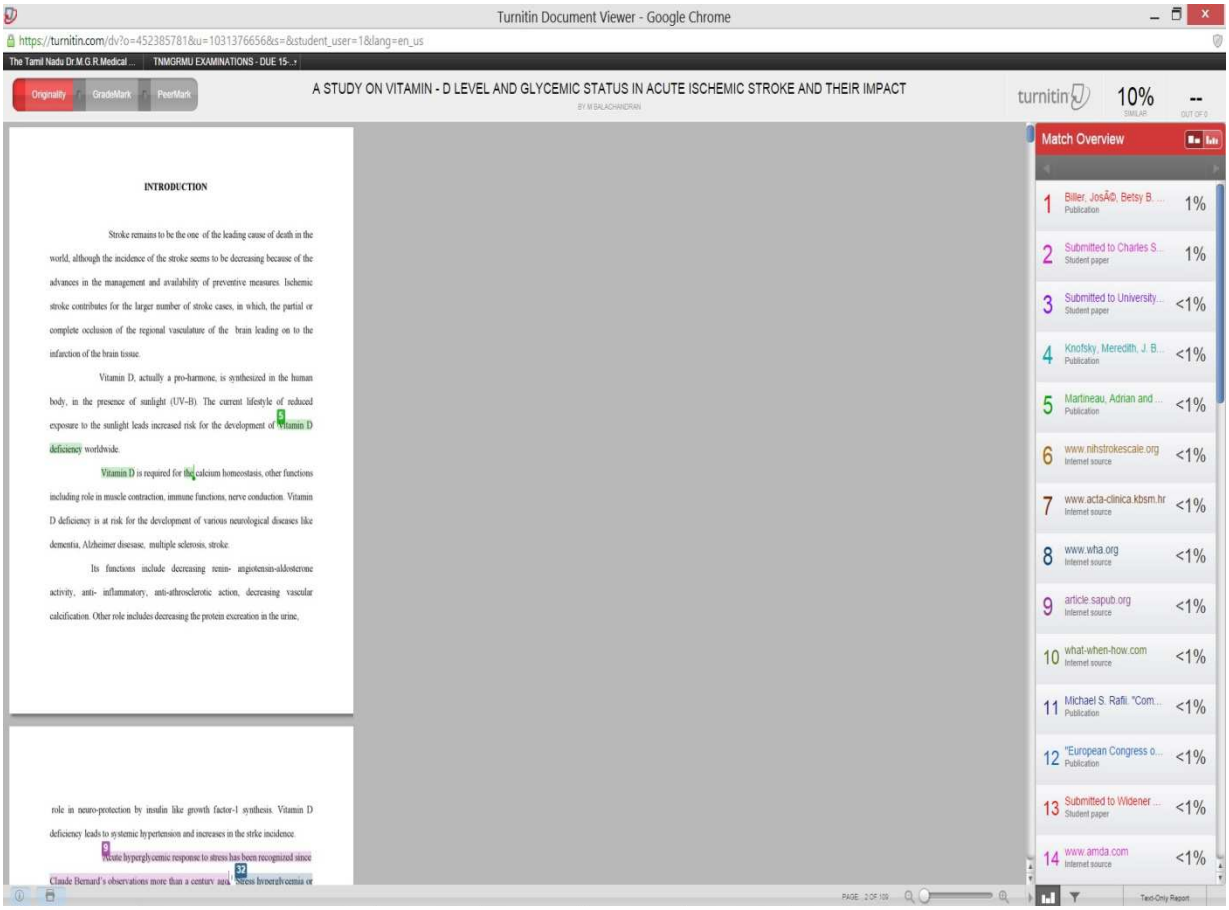
Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

14/7/14

Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN PLAGIARISM SCREEN SHOT



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INTRODUCTION

Stroke remains to be the one of the leading cause of death in the world, although the incidence of the stroke seems to be decreasing because of the advances in the management and availability of preventive measures. Ischemic stroke constitutes for the larger number of stroke cases, in which, the partial or complete occlusion of the regional circulation of the brain leading on to the infarction of the brain tissue.

Vitamin D, actually a pro-hormone, is synthesized in the human body, in the presence of sunlight (UV-D). The current lifestyle of reduced exposure to the sunlight leads increased risk for the development of Vitamin D deficiency worldwide.

Vitamin D is required for the calcium homeostasis, other functions including role in neuromuscular, immune functions, nerve conduction. Vitamin D deficiency is at risk for the development of various neurological disorders like dementia, Alzheimer disease, multiple sclerosis, stroke.

by functions include decreasing tissue angiotensin-aldosterone activity and inflammation), anti-atherosclerotic action, decreasing vascular calcification. Other risk includes decreasing the previous occurrence in the stroke,

PATIENT CONSENT FORM

Study Title : "A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Name :

Age/Sex :

Identification Number :

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination, diagnostic tests including hematological, biochemical tests and radiological tests. ❑

Signature/ Thumb impression

Patient's name and address

Signature of the investigator

Study Investigator's name

Dr. M. BALACHANDRAN

INFORMATION SHEET

We are conducting a study on **"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the **"A STUDY ON VITAMIN-D LEVEL AND GLYCEMIC STATUS IN ACUTE ISCHEMIC STROKE AND THEIR IMPACT".**

We are selecting certain cases and if you are found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator	Signature of Participant

MASTER CHART

S.NO	AGE	SEX	CBG ON ADMISSION (mg/dl)	NIHSS ON ADMISSION	INFARCT VOLUME IN < 24 HOURS (cm 3)	INFARCT VOLUME ON 3-7 DAYS (cm3)	CHANGE IN INFARCT VOLUME (cm3)	VIT-D3 LEVELS
1	65	M	98	7	15	24	9	A
2	44	M	125	6	7	15	8	A
3	48	M	117	11	12	20	8	A
4	66	M	130	7	12	29	17	C
5	60	M	455	28	38	68	30	B
6	62	M	388	21	30	53	23	A
7	55	M	103	10	12	26	14	A
8	74	M	152	15	18	38	20	A
9	48	M	130	17	18	36	18	C
10	37	M	123	10	13	19	6	A
11	74	M	413	24	20	48	28	B
12	64	M	106	12	12	27	15	A

13	68	M	108	13	16	30	14	A
14	52	F	136	18	20	33	13	B
15	58	F	135	8	6	12	6	A
16	15	F	194	14	17	37	20	C
17	38	F	96	11	11	25	14	A
18	32	F	259	12	20	48	28	C
19	75	F	176	14	18	40	22	A
20	50	F	110	14	13	28	15	A
21	73	F	114	9	16	24	8	A
22	45	F	147	15	19	33	14	A
23	40	F	166	16	16	29	13	A
24	74	F	90	10	14	28	14	A
25	59	F	137	14	27	46	19	A
26	55	F	388	21	30	53	23	A
27	85	F	231	18	28	43	25	B
28	70	F	118	8	17	23	7	A
29	18	F	122	8	18	28	10	A
30	80	F	378	23	20	47	27	A
31	60	F	113	9	10	18	8	B
32	57	F	130	6	6	10	4	A
33	45	F	132	9	18	36	18	A

34	70	F	181	18	17	32	15	A
35	45	M	174	17	18	39	21	A
36	28	M	128	11	14	28	14	A
37	40	M	126	12	11	18	7	B
38	49	M	107	8	6	13	7	A
39	45	M	199	20	17	37	20	C
40	78	M	309	23	16	38	22	A
41	64	M	186	19	15	34	19	A
42	59	M	120	14	20	32	12	A
43	84	M	124	13	14	28	14	B
44	40	M	298	24	19	36	17	A
45	84	M	210	17	22	43	19	A
46	72	M	102	15	17	30	13	B
47	58	M	217	20	25	47	22	A
48	40	M	138	16	19	41	22	A
49	52	M	102	14	16	28	12	A
50	39	M	139	11	11	28	17	A

VITAMIN D LEVELS

A - NORMAL

B - INSUFFICIENCY

C - DEFICIENCY